NICE National Institute for Health and Care Excellence

Single Technology Appraisal

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

Committee Papers

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

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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 submission** from:
   a. Sleep Apnoea Trust Association (SATA)

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

5. **Evidence Review Group** – factual accuracy check

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

7. **Technical engagement responses and personal perspectives from experts:**
   a. Graham Hill – patient expert, nominated by Sleep Apnoea Trust Association (SATA)
   b. Dr Ari Manuel – clinical expert, nominated by Lincoln Medical
   c. Dr Sonya Craig – clinical expert, nominated by British Thoracic Society

8. **Technical engagement response from consultees and commentators:**
   a. Lincoln Medical

9. **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 CARE EXCELLENCE

Single technology appraisal

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

Document B

Company evidence submission

Form B

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ID1499_Solriamfetol FormB_Redacted_17Dec	3.0	Yes	17 Dec 2020

Contents

Tables and figures

Abbreviations

AASM	American Academy of Sleep Medicine
AE	Adverse event
AHI	Apnoea hypopnoea index
ANCOVA	Analysis of covariance
BMI	Body mass index
BP	Blood pressure
BSC	Best supportive care
CCI	Charlson comorbidity index
CEAC	Cost-effectiveness acceptability curve
CEP	Cost-effectiveness plane
CFB	Change from baseline
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
CPAP	Continuous positive airway pressure
CrI	Credible interval
CSR	Clinical study report
C-SSRS	Columbia-suicide severity rating scale
DNRI	Dopamine and noradrenaline reuptake inhibitor
DVLA	Driver and Vehicle Licensing Agency
EDS	Excessive daytime sleepiness
EMA	European Medicines Agency
EMR	Electronic medical report
EPAR	European public assessment report
EQ-5D	5-dimension EuroQol
EQ-5D-3L	3-level 5-dimension EuroQol
EQ-5D-5L	5-level 5-dimension EuroQol
EQ-VAS	EuroQoL Visual Analog Scale
ERG	Evidence Review Group
ESS	Epworth sleepiness scale
EU 5	European Union Five (France, Germany, Italy, Spain, UK)
FDA	Food and Drug Administration
FOSQ-10	Functional outcomes of sleep questionnaire 10 item
HGNS	Hypoglossal nerve stimulation
HR	Heart rate

HRP	Home Respiratory Polygraphy
HRQoL	Health-related quality of life
HRU	Healthcare resource utilisation
HTA	Health technology assessment
HUI	Health utility index
HSUV	Health state utility value
ICER	Incremental cost-effectiveness ratio
ICSD-3	International Classification of Sleep Disorders, 3rd Edition
IPG	Interventional procedures guidance
IVRS	Interactive voice response system
IWRS	Interactive web response system
ITT	Intent to treat
KOL	Key opinion leader
LOCF	Last observation carried forward
LS	Least squares
LY	Life years
MAD	Mandibular advancement device
MCID	Minimal clinically important difference
MCS	Mental component summary
mITT	Modified intent to treat
MMRM	Mixed model repeated measures
MWT	Maintenance of wakefulness test
MWT40	40-minute maintenance of wakefulness test
NA	Not applicable
NHS	National health service
NHWS	National Health and Wellness Survey
NICE	National Institute for Health and Care Excellence
NR	Not reported
OLS	Ordinary least square
OR	Odds ratio
OSA	Obstructive sleep apnoea
OSAHS	Obstructive sleep apnoea hypopnoea syndrome
OTC	Over the counter
PAP	Positive airway pressure
PCS	Physical component summary
PGI-c	Patient global impression of change
PP	Per protocol
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses

PSA	Probabilistic sensitivity analysis
PSG	Polysomnography
PSS	Personal Social Services
PSSRU	Personal Social Services Research Unit
QALY	Quality adjusted life-year
qd	Once daily
QoL	Quality of life
QWB	Quality of wellbeing
RCT	Randomised controlled trial
REM	Rapid eye movement
RTA	Road traffic accident
SAHS	Sleep apnoea hypopnoea syndrome
SD	Standard deviation
SDB	Sleep disordered breathing
SE	Standard error
SF-36	36-item short-form health survey
SF-36v2	36-item short-form health survey version 2
SG	Standard gamble
SLR	Systematic literature review
SmPC	Summary of product characteristics
SNORE	Symptoms of Nocturnal Obstruction and Related Events
TONES	Treatment of Obstructive sleep apnoea and Narcolepsy Excessive Sleepiness
TTO	Time trade off
UK	United Kingdom
US	United States
VAS	Visual analogue scale
WPAI	Work productivity and activity impairment questionnaire
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

Solriamfetol is indicated to:

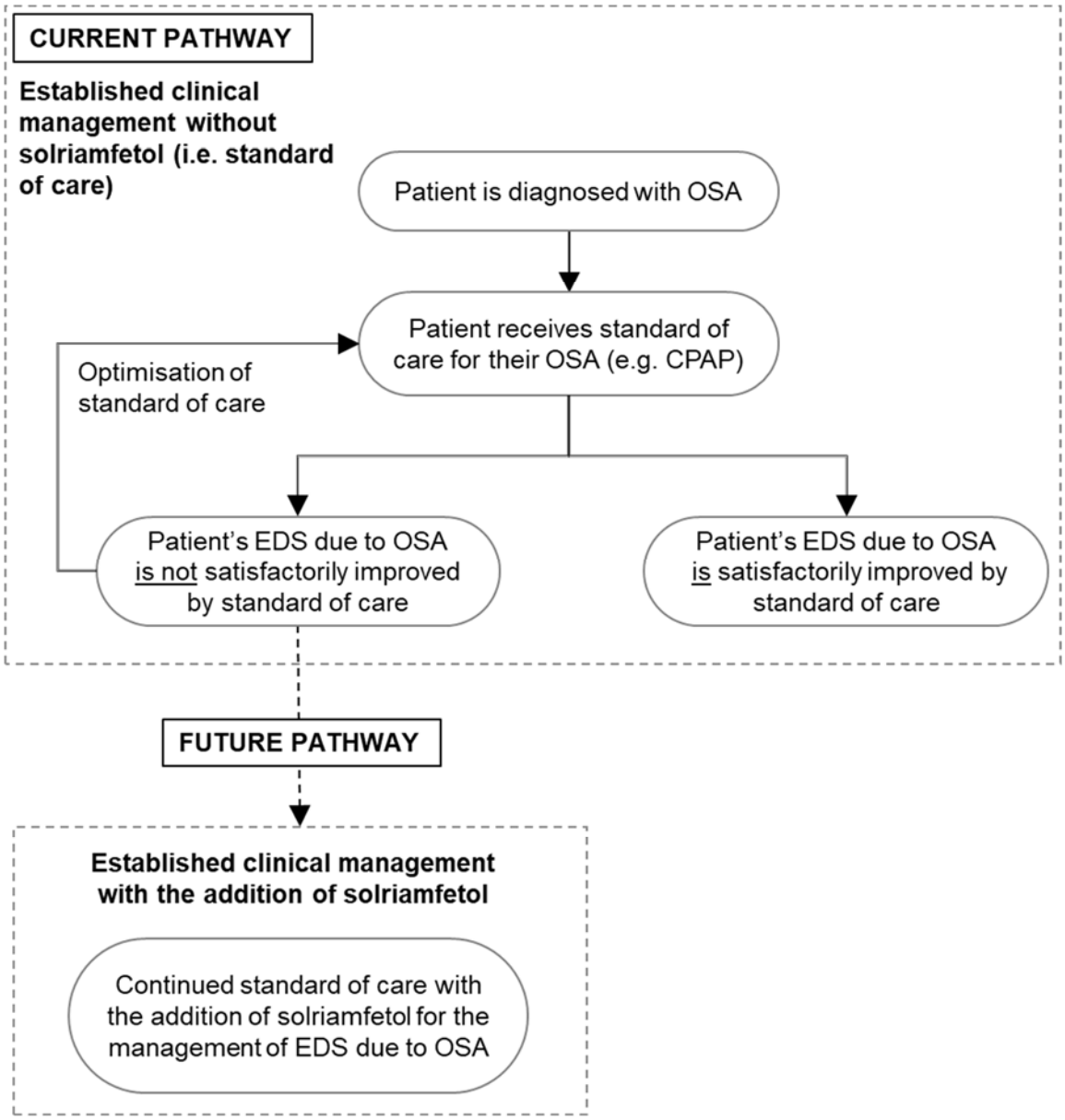
- Improve wakefulness and reduce excessive daytime sleepiness (EDS) in adult patients with obstructive sleep apnoea (OSA) whose EDS has not been satisfactorily treated by primary OSA therapy, such as continuous positive airway pressure (CPAP).
- Improve wakefulness and reduce EDS in adult patients with narcolepsy (with or without cataplexy).

This technology appraisal considers the indication for EDS in OSA only. NICE technology appraisal (TA) ID1602 considered EDS in the narcolepsy population.

This submission covers the technology's full marketing authorisation in the EDS due to OSA population. In the United Kingdom (UK), clinical practice for the management of OSA comprises a primary OSA therapy, to manage the underlying condition causing OSA. Positive airway pressure (PAP), including CPAP and nasal PAP, is the most widely used primary OSA therapy in the UK. Although PAP is not indicated to manage EDS (a common symptom of OSA), for many patients their primary OSA therapy treats both the underlying OSA and reduces their EDS. However, a small proportion of patients with OSA will continue to experience persistent EDS daily and throughout the day, despite treatment with a primary therapy, which negatively impacts their personal and professional life.

In the current treatment pathway, there are no treatment options specifically licensed to manage EDS due to OSA. As such, patients with OSA whose EDS is not satisfactorily managed by a primary OSA therapy will continue to experience the burden of their EDS. Solriamfetol therefore represents a new treatment option in the existing treatment pathway, to manage EDS due to OSA. The proposed position of solriamfetol in the treatment pathway for OSA is outlined in Figure 1.

Figure 1. Proposed positioning of solriamfetol in the OSA treatment pathway



Abbreviations: CPAP, continuous positive airway pressure; EDS, excessive daytime sleepiness; OSA, obstructive sleep apnoea.

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	Adults with OSA whose EDS has not been satisfactorily treated by primary OSA therapy, such as CPAP.	Adults with OSA whose EDS has not been satisfactorily treated by primary OSA therapy, such as CPAP.	
Intervention	Solriamfetol with or without primary OSA therapy	Solriamfetol with or without primary OSA therapy	
Comparator(s)	• Established clinical management without solriamfetol (i.e. standard of care without solriamfetol)	• Established clinical management without solriamfetol (i.e. standard of care without solriamfetol)	
Outcomes	• EDS • Fatigue • Length of life • Adverse effects of treatment • Health-related quality of life	• EDS • Adverse effects of treatment • Health-related quality of life	• Fatigue is a general symptom, variably expressed by patients in wide range of clinical settings. It is not an outcome measure assessed or used by clinicians to determine response to treatment in OSA. In addition, it was not assessed during the TONES clinical trial program. It is therefore neither relevant to this submission nor feasible to provide data regarding any potential impact of solriamfetol on it. • 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 OSA.

Abbreviations: CPAP, continuous positive airway pressure; EDS, excessive daytime sleepiness; NHS, National Health Service; NICE, National Institute of health and Care Excellence; OSA, obstructive sleep apnoea.

B.1.2 Description of the technology being appraised

An SmPC for the use of solriamfetol in the management of EDS in patients with OSA is provided in Appendix C.

Although studied in clinical trials (TONES studies) the 300 mg dose is not licensed, and has only been presented within the current submission when describing the study design and baseline characteristics of TONES trials.

Solriamfetol is a wake-promoting agent, intended to manage EDS by reducing sleepiness and improving wakefulness in patients with EDS, specifically due to OSA or narcolepsy. Further details for solriamfetol, including the indication, regulatory status, method of administration, dosing, and related costs are provided in Table 2.

To manage EDS in patients with OSA, solriamfetol is administered orally, once daily, at a starting dose of 37.5 mg and titrated depending on clinical response and tolerability, to a maximum dose of 150 mg, by doubling the dose at intervals of at least 3 days. The rationale for a 3 day interval as a minimum duration between dose titration relates to the time taken for solriamfetol to reach plasma steady state and is the standard that was used in the TONES clinical trial programme. However, it is expected that titration will occur over significantly longer periods in clinical practice. Given the uncertainty around the interval between titration in UK practice, the current submission used a conservative approach, guided by UK clinical expert input, with regards the cost of solriamfetol treatment considered in the cost-effectiveness model (Section B.3.5.1).

Table 2: Technology being appraised

UK approved name (brand name)	Solriamfetol (Sunosi®)
Mechanism of action	Solriamfetol is a centrally-acting sympathomimetic. 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 dopamine and noradrenaline reuptake inhibitor.
Marketing authorisation	• A regulatory submission was made to the EMA in November 2018. • CHMP positive opinion was received on 14 November 2019 with marketing authorisation granted by the European Commission on 16th 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 OSA whose EDS has not been satisfactorily treated by primary OSA therapy, such as CPAP. • Improve wakefulness and reduce EDS in adult patients with narcolepsy (with or without cataplexy). **This technology appraisal considers the indication for EDS in OSA only. NICE technology appraisal ID1602 considered EDS in the narcolepsy population.**
Method of administration and dosage	• Available as 75 mg and 150 mg orally-administered film-coated tablets. Administration of a 37.5 mg dose can be achieved by halving a 75 mg tablet using the score line. • The recommended starting dose in patients with OSA is 37.5 mg once daily, upon wakening. • 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 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	Other than initial BP and HR monitoring required per the SmPC, no additional tests or investigations are anticipated to be required.
List price and average cost of a course of treatment	• List price £177.52 per pack of 28 x 75 mg film-coated tablets (equating to 28 days treatment at 75 mg, or 56 days treatment at 37.5 mg; unit price £6.34 per 75 mg tablet). • 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). • The total cost per year (52 weeks) of treatment at list price would be: – £1,154 at the 37.5 mg dose (using the 75 mg tablet; 37.5 mg dose can be achieved by halving a 75 mg tablet using the score line). – £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	Not Applicable

Abbreviations: CHMP, Committee for Medicinal Products for Human Use; CPAP, continuous positive airway pressure; 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 OSA

OSA is a chronic, common, and incapacitating sleep disorder, characterised by the repeated occurrence of complete (apnoea) or partial (hypopnoea) closures of the upper airway during sleep (1-4). These apnoeic episodes are accompanied by hypoxaemia (low oxygen levels) and hypercapnia (high carbon dioxide levels) which affects regulation of the cardiovascular system and increases sympathetic nervous system activity (5, 6). OSA may also be referred to as obstructive sleep apnoea syndrome (OSAS) or obstructive sleep apnoea hypoapnoea syndrome (OSAHS) reflecting the range of symptoms which a patient with OSA may suffer.

OSA severity is typically measured using the apnoea hypopnoea index (AHI), which is calculated from the sum of apnoeas and hypopnoeas, divided by the number of hours of sleep; an AHI > 5 is used to diagnose OSA, and OSA severity is typically classified as mild OSA at AHI 5–15, moderate OSA at AHI 15–30 and severe OSA at AHI greater than 30 (1). The cause of OSA can vary widely (7), however the major predisposing factors are obesity (5), male sex, and older age (8). Other risk factors include a sedentary lifestyle, hypertension, alcohol use, smoking, anxiety, depression, low socioeconomic status, chronic pulmonary disease, and diabetes (9).

The oxygen desaturation caused by apnoeic episodes, and the associated increased respiratory effort, eventually leads to disruption of sleep (awakening) (1-4). Upon awakening, the muscles controlling the patient's upper airway are reactivated and reopen the airways (1), however a patient may awaken and fall back to sleep without realising they awoke, and may therefore report no problems with their sleep (10, 11). The recurrent pattern of obstructed breathing and cardiovascular strain can have extensive physiological consequences, placing patients at risk of hypertension, cardiovascular disease, cardiac arrhythmias and diabetes (12-14). Despite the patient's unawareness of their condition, if their OSA remains undiagnosed and/or untreated, the consequences of OSA (including chronic intermittent hypoxaemia, sleep fragmentation, haemodynamic disturbance, and alterations in sympathetic activity) may lead to death (15). Untreated patients with OSA have an estimated 22–

25% greater rate of hospital admissions or treatment days due to cerebrovascular, or cardiovascular causes, compared with CPAP-treated patients (16).

Although patients may be unaware of their night-time symptoms (i.e. loud snoring, or gasping during sleep), the fragmented sleep negatively impacts their sleep quality, and patients may become aware of daytime symptoms of OSA, which include EDS, napping, decreased energy, irritability, feeling unrefreshed or having headaches upon awakening, reduced enjoyment of usual activities, and impaired work performance (17-20).

Overview of EDS due to OSA

EDS is a prominent symptom of OSA, occurring daily and throughout the day, and represents a major complaint in patients with OSA (4, 21, 22). Of note, patients' levels of EDS are independent of their OSA severity (as defined using AHI scores) (23-26), indicating that the symptom of EDS must be managed independently of the underlying OSA – this effect was observed in TONES 3, where the trial population had median AHI scores in the normal range but substantial levels of EDS (Table 7). This effect has been demonstrated in US studies of modafinil (not licensed for OSA in the UK) for managing EDS, which show that despite optimal CPAP treatment reducing AHI scores to the normal range, these optimally treated patients maintained high EDS levels that were subsequently reduced to normal levels following treatment with a wake-promoting agent (26).

The nature of EDS due to OSA is severe and pervasive, and greater levels of EDS are associated with increased levels of impairment (4, 27). The severe and chronic consequences of EDS have far-reaching negative impact(s) on the patient's daily activities, physical health and cognitive function (including vigilance, attention, and short- and long-term memory) (4, 22, 28-31). EDS in patients with OSA is a significant and independent predictor of hypertension, cardiovascular disease and coronary artery disease (29).

OSA with EDS is associated with a variety of comorbidities including major depressive disorder, gastroesophageal reflux disease, asthma, diabetes, hypertension, insomnia, cardiovascular, pulmonary, or psychiatric disease (32-34).

The rates of some comorbidities are higher in people with OSA with EDS, compared to people with OSA but without EDS (32, 34).

Epidemiology of OSA in the UK

An estimated 1.5 million adults in the UK have OSA (31), equating to 2.32% of the overall population; of these approximately 22% are diagnosed and treated for their OSA (31). Of the overall OSA population, approximately 55% of patients have mild OSA (AHI ≤15) and 45% have moderate-to-severe OSA (AHI >15) (3). In 2008, the reported prevalence of OSA in UK adults (aged 30 to 65 years) was 2% in women, and 4% in men (35). The female bed partners of male patients are more likely to perceive and report snoring or abnormal breathing patterns, compared with the male bed partners of female patients (36), which may explain some of the higher prevalence in men.

In a UK Sleep Survey (adults ≥18 years) the rates of "OSA", defined as the self-reported presence of snoring plus breathing pauses during sleep was 5.6% in 2015 (37). However, the survey reflects participant reported symptoms, relied on patient accuracy, and did not require participants to have an objective/formal diagnosis of OSA, which is likely to have significantly inflated the true prevalence rate in the survey. Using data from 239 National Health Service (NHS) administrative areas across the UK[a], the highest predicted prevalence rates of OSA are in Wales, the North East, and parts of East Anglia and Lincolnshire, and the lowest predicted prevalence rates are in larger urban areas (with younger mean population age) such as London (38).

Epidemiology of EDS due to OSA in the UK

Not all patients with OSA suffer from EDS, and vice versa – as described above there will be a proportion of patients who are completely unaware of their OSA, most likely because they do not experience any EDS. Data on the incidence and prevalence of EDS due to OSA in the UK are lacking, and establishing the true

[a] Information from 213 administrative areas in England, 14 in Scotland, 7 in Wales and 5 in Northern Ireland was used to map five factors commonly associated with OSA: obesity, diabetes, age, hypertension, sex.

prevalence of EDS due to OSA is problematic due to the multiple potential causes of EDS (e.g. central nervous system disorders, shift work disorder, insomnia) (10).

Patient and partner burden of EDS in patients diagnosed with OSA

EDS due to OSA affects the patient's physical health, social functioning, emotional and mental well-being, cognition, family life, daily function and work productivity (19, 28, 39-41). Due to their sleepiness, patients with OSA and EDS report that they force themselves to complete activities from their daily routine and experience limitations in their family relationships, socialising, professional life, and exercise/leisure (42-44). In a large scale survey, the aspect of life considered most important for health-related quality of life (HRQoL) in a random sample of people in Great Britain was relationships with family/relatives; for those respondents who were living with a chronic illness, the most influential aspects of life on HRQoL were: the ability to get out and about, being able to work/find a job, and effects on social life/leisure activities (45). EDS due to OSA thus directly affects several aspects of life that are considered most important for HRQoL in Great Britain (45), indicating that patients with EDS due to OSA are living with a symptom that substantially negatively impacts all aspects of their daily life and consequently reduces their HRQoL.

Unfortunately, despite the widely-accepted burden and impact of EDS in other indications, such as EDS due to narcolepsy (46-48), the EDS due to OSA is often passed off as a minor problem in the context of the primary reason for patient referral (i.e. the underlying OSA) (42). There is limited research specifically examining the impact of EDS due to OSA, in isolation from the overall burden of OSA and its related symptoms. A qualitative analysis[b] of the burden of EDS due to OSA, carried out on behalf of Jazz Pharmaceuticals (40, 49, 50), (hereafter "Burden of EDS Study") found that patients with EDS due to OSA have extreme levels of tiredness, describing their symptoms as a "brain fog", "sleepiness", or "feeling like they never get enough sleep" (regardless of the number of hours of sleep). The impact of their

[b] Six semi-structured focus groups were conducted with adults (n=42) who experienced excessive sleepiness associated with OSA in three U.S. cities. All focus groups were conducted in-person at focus group facilities. The semi-structured focus group discussion guide was developed based on a literature review designed to elicit participants' experiences with ES across several dimensions of HRQoL. Due to the semi-structured nature of the interviews, not all participants were asked all questions or reported experiencing treatment-related impacts.

EDS was pervasive with 74% of patients reporting they needed to take naps, 67% reporting low energy levels and 62% reporting they feel asleep during activities: [redacted]. As a result of the burden of their EDS, 90% of participants reported that EDS affected their social lives/relationships, 21% said that they planned their day around their EDS, and 17% said they had a decreased ability to provide childcare, or do household chores. The responses to the Burden of EDS Study demonstrate the extensive and persistent impact of EDS on the daily lives of patients with EDS due to OSA (40, 49). The impact of EDS observed in the Burden of EDS Study is supported by KOLs (from UK KOL interviews and Advisory Boards[c], hereafter "UK KOL Evidence") who describe the burden of EDS using terms such as "profoundly tired", "disabling" and "under recognised", and acknowledge the need for new treatment options in patients who have persistent EDS (51).

People diagnosed with OSA who have EDS have significantly lower emotional health and energy compared with people with OSA without EDS (52). In recently diagnosed (but yet untreated) patients with OSA, the prevalence of anxiety was significantly higher in those patients with OSA and EDS compared with patients with OSA who did not have EDS (53). The far-reaching impact of EDS due to OSA substantially reduces the patient's quality of life (QoL) and a body of evidence in studies of patients diagnosed with OSA shows that EDS due to OSA is associated with reduced QoL scores on the 36-Item Short Form Health Survey (SF-36) (30, 54-56). The presence of EDS in patients diagnosed with OSA is associated with greater levels of physical and mental health impairment, compared with controls without OSA and patients with OSA who do not have EDS (32). Furthermore, higher levels of EDS are associated with increased burden, with incremental impairment in physical and mental health, and work productivity observed in patients with OSA who have higher levels of EDS, compared with lower levels of EDS (43).

[c] Feedback from UK KOLs was gathered through Adboards and Medical Science Liaison face-to-face interviews, designed to understand more about the current treatment pathway in OSA, the burden to patients, the assessment of response to treatment, and the treatments used as part of standard of care in the UK.

The effects of EDS in patients with OSA can extend to the patient's work and professional life: EDS and its associated effects on cognition can place patients at increased risk of a work disability (57) or occupational injury (58). The EDS caused by OSA contributes significantly to work limitations, in particular for domains of time management, mental and interpersonal function, work output, and physical demand (27). Patients with EDS due to OSA report a significantly greater impact on their work productivity compared with patients with OSA who do not have EDS, and there is a relationship between increasing levels of EDS and greater impairments in work productivity (43). Participants in the Burden of EDS Study reported that the EDS due to their OSA impacted their professional lives, with [redacted]% reporting EDS currently impacted their work, and [redacted] reporting it previously impacted their work (49). Furthermore, 69% of respondents reported that their EDS impacted their ability to stay awake at work, 52% had problems with detail-oriented tasks, and 26% reported limitations in the type or work/job they could do , indicating that multiple aspects of work are affected by EDS due to OSA (40).

As discussed above, patients with OSA may report difficulties with their family life and the impact of OSA-related symptoms on the patient's family may be so severe that the patient's family urge the patient to seek help for their OSA symptoms (17, 59); in a UK survey, 50% of patients reported that their partner was the first to notice their symptoms (17). The symptoms of OSA, including EDS due to OSA, affect both the patient and their partner (41, 54). Several studies demonstrate that the partners of patients with OSA have reduced QoL across both physical and mental domains, compared with the normal population (54, 59-61).However many of these studies report the overall burden of OSA (not the impact of EDS itself) on the partner's QoL, whereas fewer studies specifically examine the impact of EDS due to OSA on the partner's QoL. Based on the limited studies available, the patient's EDS due to OSA has a substantial negative impact on their partner's QoL. The partners of patients with EDS due to OSA reported feeling frustrated, irritated, angry, dissatisfied with their marriage, and reported 'conflict over children rearing' as a particular issue in their relationship (62). EDS due to OSA contributes to relationship dissatisfaction and relationship problems between patients and their partners, and higher ESS scores are associated with worse relationship quality; furthermore, patients whose

symptoms of OSA were not controlled had worse scores than those patients who were receiving treatment (63). The negative correlations between patient's level of EDS and relationship satisfaction indicate that the effects of EDS due to OSA extend beyond that patient, and demonstrate that treatment is necessary to positively impact both the patient and partner QoL.

Despite the clear and pervasive impact of OSA, or EDS due to OSA, on the patient and their partner, some patients may self-report 'normal' QoL (54, 61, 64). The reasons for this effect are unknown, but may indicate patient adaptation to their EDS – in studies on patient/partner dyads, patients with OSA self-reported normal ESS and QoL scores, however their partners rated the patients' ESS and QoL as abnormal, indicating that patients may underestimate the impact of EDS on their life and adjust their expectations of health accordingly (23, 54). Some patients are unaware of their OSA and/or OSA-related night-time symptoms, however their partners are acutely aware of these night-time symptoms (which may be so impactful to the partner, they that encourage the patient to seek help) (61). As a consequence of their own interrupted sleep, the partners may be more alert to the impact of the patient's daytime symptom of EDS on the patient, their relationship, and their family.

UK KOL Evidence supports the occurrence of adaptation in patients with EDS due to OSA – KOLs report that patients adapt so much to their EDS that they are unaware of the impact that it is having on their QoL, daily function and work productivity (51). Furthermore, there is some evidence of adaptation to EDS by the patient's partner – despite having no disutility at baseline, the partners of patients with OSA achieved significant improvements in QoL once the patient was receiving PAP treatment (54, 61). This indicates that partners may adapt their expectations of their own health/QoL according to the patient's OSA-related symptoms; they are less likely to report any disutility to themselves but more likely to report the impact of these symptoms on the patient (for example their EDS affecting daily activities). This highlights an insidious burden of EDS in both patients with EDS due to OSA, and their partners; the patient and partner's adapted expectations of health/QoL masks the OSA-related impact to QoL. This discrepancy between how the patient and their partner rate the impact of OSA or OSA-related EDS to daily life, and/or their inability

to recognise the impact of the condition may contribute to further discord in their family life or relationships, thus increasing and extending the burden of disease.

EDS is associated with drowsy driving and falling asleep while driving, and with an increased risk of having a road traffic accident (RTA) (65-67). In a survey of UK patients with OSA (2015), 11% of respondents had fallen asleep while driving and 2% admitted having a RTA due to their EDS (17). As a result of these increased risks, there are strict regulations and monitoring requirements in the UK for both commercial and non-commercial drivers with EDS due to OSA (68-70). Unfortunately, the neurobehavioral deficits in patients with OSA are not always fully reversed by primary OSA therapy and impairments in driving performance can persist (71) which highlights the clear unmet need for a pharmacological treatment option for the management of EDS due to OSA that can improve wakefulness.

Persistent EDS due to OSA may occur despite optimal standard of care

In UK clinical practice, standard of care for OSA (beyond general lifestyle adaptations) consists of a primary OSA therapy (e.g. CPAP, oral appliances, upper airway stimulation or surgery) to manage the underlying OSA. Primary OSA therapies are not indicated to manage EDS due to OSA, but for a large proportion of patients, a primary OSA therapy may adequately reduce their EDS (25, 26, 56, 63, 72). It is important to recognise that even when primary OSA therapies effectively manage the underlying OSA (i.e. achieve normal AHI scores), this "optimal effective treatment" refers to management of the underlying OSA. However, despite having an AHI score in the normal range, some patients continue to experience substantial EDS (23-26, 73). This has been demonstrated in several studies in which patients who were using a primary OSA therapy (e.g. CPAP) at an optimal effective level[d] experienced persistent EDS (25, 52, 72, 74, 75). As described by the Assessment Group Report for NICE TA139 (76), and in multiple studies (25, 74, 77-79), primary OSA therapies typically achieve mean absolute reductions in ESS scores of 2–4 points. Based on this mean reduction of 2–4 points, it is likely that many patients with lower levels of EDS (i.e. ESS 11–13) prior to commencing a primary OSA

[d] Optimal effective levels of PAP use are typically defined as ≥4 hours per night

therapy would achieve normal ESS scores (ESS ≤10) using that primary OSA therapy, whereas the patients with higher baseline levels of EDS (i.e. EDS ≥14) prior to commencing a primary OSA therapy will be less likely to achieve normal ESS scores after using a primary therapy such as CPAP. As such, patients with higher baseline ESS scores at OSA diagnosis may experience high levels of persistent EDS despite using a primary OSA therapy, and therefore require an additional treatment to reduce their EDS or achieve normal ESS scores (≤10).

The management of EDS in adult patients with OSA is very specific to the individual and therefore highly variable (80). It is unknown what proportion of patients with OSA will experience EDS following optimal treatment with a primary OSA therapy, but studies estimate that 6–22% of patients who are compliant to CPAP will experience persistent EDS that cannot be explained by any other cause (52, 56, 75, 81). This is consistent with UK KOL Evidence, which estimated values of 4–20%, however UK KOLs report that all patients with persistent EDS will receive extensive additional tests and investigations to identify the source of EDS, and after this further assessment, only 2–6% of patients will have true unexplained EDS (51). There is thus an unmet need in the UK for a treatment specifically indicated to reduce sleepiness and improve wakefulness in patients with OSA whose EDS is not satisfactorily treated by a primary OSA therapy (e.g. CPAP).

Healthcare burden of OSA and EDS

OSA represents a substantial economic burden to healthcare systems (38, 82). For example, in 2014, the estimated annual saving[e] to the NHS was £55 million if all patients with moderate-to-severe OSA were diagnosed and treated with CPAP (compared to no patients being diagnosed and treated) (3, 83). However, although primary OSA therapies (such as CPAP) can reduce the healthcare burden associated with the underlying OSA, they are not specifically indicated to manage EDS. Therefore, the proportion of patients with OSA who experience persistent EDS due to OSA, will return to the healthcare services to seek treatment for this symptom. At present there are no treatment options available for these patients, and the EDS

[e] Savings were calculated based on the reduction in acute events such as stroke, cardiovascular events, RTAs

due to OSA is often passed off as a minor problem with regards the primary reason for referral (the underlying OSA) (42) thus this patient population continues to contribute to the burden of EDS due to OSA on healthcare systems.

The direct and indirect economic burden of EDS due to OSA remains largely unrecognised, and there is limited information on the healthcare burden of EDS due to OSA (84). Two large-scale studies (US, European Union [EU] 5[f]) demonstrated that healthcare resource utilisation (HRU) is significantly greater in patients with OSA and EDS, compared with patients with OSA without EDS (43, 85). Compared with patients with no EDS, the US study reported that patients with EDS had significantly more physician visits per year than those without EDS (odds ratio [OR] 1.25; 95% confidence interval 1.0-1.57) (85). The EU5 study examined whether the burden increased with increasing severity of EDS and showed that the burden was driven by higher levels of severity; patients with moderate or severe EDS had significantly more physician visits, and that patients with severe EDS had significantly more emergency room visits and hospitalisations (43).

Guidelines and limitations for current treatments of OSA and EDS

There are currently no treatments in the UK that are specifically licensed to manage EDS due to OSA. Likewise, there are no national guidelines on the management of EDS but the National Institute for Health and Care Excellence (NICE) has published three sets of guidance on the management of OSA (not specific to EDS) in the UK:

- NICE Interventional Procedure Guideline [IPG] 598 (2017): Hypoglossal Nerve Stimulation (HGNS) for moderate to severe OSA (86). IPG598 recommends that due to the limited quantity and quality of safety and efficacy evidence for this procedure, HGNS should only be used with special arrangements for clinical governance, consent and audit or research.
- NICE TA139 (2008): CPAP for the treatment of OSAHS (87). TA139 recommends CPAP as a treatment option for adults with moderate or severe symptomatic OSAHS, or as a treatment option for adults with mild OSA only if they have symptoms that affect their quality of life and ability to go about their

[f] EU 5: France, Germany, Italy, Spain, UK

daily activities, and lifestyle advice and any other relevant treatment options have been unsuccessful or are considered inappropriate.

- NICE IPG241 (2007): Soft-palate implants for obstructive sleep apnoea (88). IPG241 recommends that soft-palate implants should not be used in the treatment of OSA, due to inadequate evidence of efficacy.

NICE guidelines on "OSAHS and obesity hypoventilation syndrome in over 16s" are expected in November 2020, however due to their early stage of development, pharmacological products for OSA[g] will not be considered in these guidelines (89).

The above NICE guidance documents describe three potential treatment options for managing the underlying cause of OSA (i.e. the obstruction) in UK practice; typically clinicians advise that patients undergo lifestyle changes such as improved sleep hygiene, weight loss, alcohol avoidance, or changing sleeping position, in order to improve their symptoms of OSA (86, 88, 90). CPAP is considered the first-line therapy for OSA across the UK and an estimated 230,000 patients in the UK use CPAP therapy (87, 91); however CPAP manages the underlying airway obstruction in OSA, and for patients who use CPAP at an effective optimal level but continue to experience persistent EDS, there are no subsequent treatments to manage their EDS nor any guidelines on managing their EDS.

Modafinil was previously licensed to manage EDS due to OSA, but this indication was removed by the European Medicines Agency (EMA) in 2010, following a review procedure under Article 31 of Directive 2001/83/EC, which concluded that the benefits of modafinil-containing medicines do not outweigh the risks in the OSA population (92). As such, OSA patients with EDS have no subsequent treatment options to manage their symptom and will continue to experience the burden of their EDS, remaining at risk of injury, ill health, and poor quality of life.

[g] It is unclear whether this refers pharmacological products for OSA generally or specifically EDS due to OSA

Unmet need in patients with residual EDS due to OSA

The burden of OSA and the burden of EDS due to OSA are substantial, pervasive and life-long. The management of EDS in adult patients with OSA is very specific to the individual and therefore highly variable (80). Although primary OSA therapies such as CPAP are available to treat the underlying cause of OSA, and may contribute to some reduction in EDS, solriamfetol is currently the only treatment option specifically licensed and indicated to reduce EDS and improve wakefulness in patients with EDS due to OSA. The addition of solriamfetol to UK clinical practice addresses an unmet need for managing EDS in patients with OSA, including patients with EDS that persists after optimal effective use of a primary OSA therapy, both of which are populations for whom there is no further treatment option to manage their EDS. Solriamfetol offers a new treatment option, with rapid onset, robust and durable efficacy that is sustained with continued treatment, and which has low potential for abuse and a well-characterised safety profile. These patients have a clear unmet need for treatment to manage their EDS, with UK KOLs reporting that EDS is extremely disabling. Furthermore, KOLs use terms such as “hugely”, “immense” and “massive” when describing how patients valued having their EDS managed, indicating the importance of access to an effective treatment option for managing EDS due to OSA.

B.1.4 Equality considerations

According to the “Health Equity in England Report”, health inequality in the UK continues to widen despite medical advancements and the ongoing improvements in health care services (93, 94). Wealth is directly and indirectly associated with good health, if you are wealthier you are therefore more likely to be healthier (94). Furthermore, work is an important factor in good health and wellbeing, and good health allows an ability to work and gives a sense of security, which in turn positively impacts mental and physical health (94).

There is evidence of a link between lower socioeconomic status and greater impact of OSA (93, 95, 96). EDS due to OSA substantially impacts patients’ careers and work productivity (27, 43, 49), thus the impact of EDS due to OSA on ability to work and work productivity may disproportionately impact the careers (and consequently

health) of patients with a lower socioeconomic status. Low wages, benefit cuts and the growth of part-time and insecure work, have increased rates of in-work poverty (94), and patients with EDS due to OSA, including those with in-work poverty, are therefore at risk of reduced health as a result of their reduced work ability and security. These patients stand to benefit from a treatment to manage their EDS, which may aid them in joining the work force, returning to work, or to acquire roles with more stability and security, higher salaries, greater career progression opportunities, and this may subsequently increase their household income, and indirectly improve their health.

B.2 Clinical effectiveness

Key explanations relating to primary OSA therapy use and compliance to this therapy within this submission.

For enrolment into TONES 3 (Treatment of Obstructive sleep apnoea and Narcolepsy Excessive Sleepiness) there were two eligibility criteria relating to OSA therapy:

1. "Use of a primary OSA therapy": patients in TONES 3 were required to (a) be currently using ([redacted]) a primary OSA therapy (PAP, oral pressure therapy, oral appliances, upper airway stimulation), (b) have prior use (historical use of ≥1 primary therapy for ≥4 weeks of usage with ≥1 documented adjustment to optimise the primary therapy [e.g., different mask, pressure, or modality]) of a primary OSA therapy, (c) have a history of surgical intervention to treat OSA symptoms. These groups were not mutually exclusive, and patients could meet one or more criteria (i.e. be compliant and have a history of surgical intervention).
2. "Stable use": patients were required to have been maintaining a consistent level of use **or** non-use of their primary OSA therapy for [redacted] prior to study entry, or have a history of surgical intervention to treat OSA symptoms.

Once enrolled, compliance to primary OSA therapy was then assessed at baseline and throughout the trial based on the following definitions:

3. "Compliant" refers to the subgroup of patients who were using a primary OSA therapy at study entry (per 1a above) **and** who were using their primary OSA therapy at or above an effective level, as defined in the study protocol; this effective level (i.e. compliance) was defined as (a) PAP use ≥4 hours/night on ≥70% of nights, or (b) historical report (with investigator concurrence) of oral appliance use

on ≥70% of nights, or (c) receipt of an effective surgical intervention for OSA symptoms.

4. "Non-compliance" refers to the subgroup of patients who were (a) not using a primary OSA therapy at study entry (1b above), or (b) who were using their primary OSA therapy at an ineffective level (defined as any level below that specified in 3a–b above), or (c) had receipt of a surgical intervention deemed no longer effective **and** the absence of compliant device use (per 3a–b above).

Note: compliance is **not used** within this submission to refer to exposure to the test intervention, i.e. solriamfetol exposure.

B.2.1 Identification and selection of relevant studies

As it is a new pharmacological treatment, the clinical evidence for solriamfetol in the management of EDS due to OSA that is of relevance to the current appraisal comprises the solriamfetol clinical trial programme (sponsored by Jazz Pharmaceuticals) used to support solriamfetol's marketing authorisation application. In addition, there are no active pharmacological treatments within the company decision problem. As such, a clinical systematic literature review (SLR) to identify available randomised controlled trial (RCT) evidence has not been presented.

B.2.2 List of relevant clinical effectiveness evidence

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 OSA or narcolepsy. In addition, two Phase 2 trials have been conducted in patients with narcolepsy (not described in this submission).

- 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 OSA and narcolepsy (including a 2-week

placebo-controlled, randomised-withdrawal phase after patients had completed ≥6 months of treatment with solriamfetol).

This submission is for solriamfetol for EDS in OSA.

- The primary comparative data are from the Phase 3 pivotal study TONES 3, which provides evidence across the full licensed dose range (37.5 – 150 mg) to be used in clinical practice, as outlined in the summary of product characteristics (SmPC; Appendix C).
- Long-term data comes from the Phase 3 study TONES 5 (which includes data on the unlicensed 300 mg dose of solriamfetol).
- TONES 4 is also included to provide comparative evidence for the impact of solriamfetol discontinuation on maintenance of treatment efficacy; however with a smaller population and limited to testing of the solriamfetol 75 mg, 150 mg and unlicensed 300 mg doses, it is considered as supporting evidence only.
- The three TONES studies in OSA are summarised in Table 3.

The pivotal trial supporting the treatment of EDS in narcolepsy (TONES 2) was considered in the technology appraisal of solriamfetol for treating EDS caused by narcolepsy (ID1602).

Table 3: Clinical effectiveness evidence

Study	TONES 3 (Study 14-003)	TONES 5 (Study 14-005)	TONES 4 (Study 14-004)
Data sources	**Key data sources:** CSR (97); Schweitzer 2019 (98); Schweitzer 2020 (73); Weaver 2020a (99); Weaver 2020b (100). **Supporting sources:** Not Applicable	**Key data sources:** CSR (101); Malhotra 2019 (102) **Supporting sources:** Weaver 2019 (103)	**Key data sources:** CSR (104); Strollo 2019 (105) **Supporting sources:** Not applicable.
Study design	Phase 3, multicentre, randomised, double-blind, placebo-controlled, 5-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)	Phase 3, multicentre, double-blind, placebo-controlled, 2-arm parallel-group, 6-week, randomised-withdrawal study of safety and efficacy
Population	Adults (18–75 years) with EDS associated with OSA	Adults with EDS associated with OSA or narcolepsy who completed:† TONES 2, TONES 3, TONES 4, or Phase 2 studies (TONES 1, ADX-N05 201, 15-004, 15-005)	Adults (18–75 years) with EDS associated with OSA
Intervention(s)	qd, oral: • Solriamfetol 37.5 mg (n=58) • Solriamfetol 75 mg (n=62) • Solriamfetol 150 mg (n=117) • Solriamfetol 300 mg (unlicensed; n=118)	qd, oral (n=643 in open-label phase and n=140 in randomised-withdrawal phase): • Solriamfetol 75 mg • Solriamfetol 150 mg • Solriamfetol 300 mg (unlicensed)	Titration (2-weeks; n=174) and stable-dose (2-weeks; n=157) phases: • Initiate with qd, oral solriamfetol 75 mg. Titrate to and stabilise at maximal tolerated dose of 75 mg, 150 mg or (unlicensed) 300 mg . Withdrawal phase (n=62), qd, oral: • Solriamfetol 75 mg • Solriamfetol 150 mg • Solriamfetol 300 mg (unlicensed)
Comparator(s)	• qd, oral placebo (n=119)	• 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)	• Withdrawal phase, qd, oral placebo (n=62)

Study		TONES 3 (Study 14-003)	TONES 5 (Study 14-005)	TONES 4 (Study 14-004)
Indicate if trial supports application for marketing authorisation	**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 and patient level data for use in the model	Provides long-term (up to 1 year) data	Provides supporting comparative efficacy and safety evidence to support the evidence from TONES 5
Reported outcomes specified in the decision problem‡ §		• EDS (**ESS**/MWT) • HRQoL (FOSQ-10, SF-36, **EQ-5D-5L**) • 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)	• EDS (**ESS**/MWT) • HRQoL (FOSQ-10) • 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 • WPAI:SHP	• PGI-c scale • CGI-c scale

Abbreviations: AE, adverse event; CGI-c; Clinical Global Impression of change; CSR, clinical study report; EDS, excessive daytime sleepiness; EQ-5D-5L, 5-level 5-dimension EuroQoL; 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; qd, once daily; SF-36, Short-Form 36-Item Health Survey; 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 or TONES 3 (B.2.6.1) formed Group A; patients who completed TONES 4 (B.2.6.3) or the Phase 2 studies TONES 1, ADX-N05 201 (Phase 2a study for EDS in narcolepsy (106)), Study 15-004 or 15-005 (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 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 treating EDS in adults with OSA consists of TONES 3, TONES 5 and TONES 4.
- TONES 4 is included here as a supporting RCT for the non-RCT TONES 5, because both trials contained a 2 week randomised withdrawal phase to assess the impact of solriamfetol withdrawal on treatment efficacy.

Study design

- TONES 3 (Phase 3, 12-week, double-blind, randomised, placebo-controlled study) was the pivotal RCT for solriamfetol in OSA, and provided data for solriamfetol 37.5 mg, 75 mg, 150 mg and (unlicensed) 300 mg doses, 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 on 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).
- TONES 4 (Phase 3, 12-week, double-blind, randomised, placebo-controlled study) provides supporting evidence for the effect of withdrawal of solriamfetol 75 and 150 mg and (unlicensed) 300 mg daily doses, compared with placebo, on solriamfetol efficacy in treating EDS.

Patients enrolled

- TONES 3 enrolled patients with OSA (diagnosed according to the International Classification of Sleep Disorders, 3rd Edition [ICSD-3] criteria) who had EDS (ESS score ≥10) and difficulty maintaining wakefulness, as defined by a mean sleep latency <30 minutes, based on the mean of the first four trials of the Maintenance of Wakefulness Test (MWT).
- In TONES 5, patients were enrolled from previously completed solriamfetol clinical trials, including patients with OSA or narcolepsy (diagnosis was as per the parent study criteria).
- TONES 4 enrolled patients with OSA (diagnosed according to the ICSD-3 criteria) who had EDS (ESS score ≥10) and difficulty maintaining wakefulness (mean sleep latency <30 minutes, based on the mean of the first four trials of the MWT).

Overall findings

- As an oral wake-promoting agent, solriamfetol has shown dose-related and clinically and statistically meaningful reductions in EDS in 614 unique patients with OSA across the clinical trial programme (including patients who received the unlicensed 300 mg dose).
- Clinical benefit versus placebo has been demonstrated using validated subjective and objective outcome measures including the ESS, MWT, Patient Global Impression of Change (PGI-c), Clinical Global Impression of Change (CGI-c), and 10-item Functional Outcomes of Sleep Questionnaire (FOSQ-10).
- Evidence from TONES 3, the non-RCT TONES 5 and the supporting RCT TONES 4, demonstrated the overall safety and tolerability of solriamfetol, and showed that long-term treatment has a consistent safety and tolerability profile to that observed in shorter-term trials.
- The safety profile for solriamfetol is consistent with its pharmacology and is what would be expected for a dopamine and noradrenaline reuptake inhibitor (DNRI). Solriamfetol within its proposed therapeutic dose range in OSA (37.5, 75 and 150 mg) is well tolerated by most patients, and in general, the adverse events (AEs) of solriamfetol occur early on in treatment, are dose-related and appear to be reversible.
- The clinical trial programme demonstrated that the effects of solriamfetol on EDS in OSA 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 (standard deviation [SD]) exposure in OSA (including the unlicensed 300 mg dose) was [redacted] in TONES 5.

TONES 3 (Pivotal comparative Phase 3 study)

- Solriamfetol 37.5, 75 and 150 mg reduced sleepiness and/or increased the ability to maintain wakefulness, in patients with EDS due to OSA versus placebo, as demonstrated by:
  - A reduction in EDS, shown by a significant decrease in subjective ESS score from baseline to week 12 for the solriamfetol 37.5, 75 and 150 mg doses (least squares [LS] mean difference vs. placebo of -1.9, -1.7 and -4.5, respectively; all $p<0.05$).
  - 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 37.5, 75 and 150 mg (LS mean difference vs placebo of 4.5, 8.9 and 10.7 minutes, respectively; all $p<0.01$).
- The magnitude of ESS and MWT effects was generally dose-dependent, observed as early as week 1 and maintained over the study duration (12 weeks).
- Normal ESS scores (ESS ≤10; see Table 6) were achieved by 51.8%, 55.2% and 70.7% of patients in the solriamfetol 37.5 mg, 75 mg and 150 mg groups, compared with 37.7% in the placebo group.
- At week 12, significant improvements in wakefulness versus placebo were apparent in each of the individual five MWT trials throughout the day for solriamfetol 75 and 150 mg (nominal $p<0.05$). For the solriamfetol 37.5 mg dose, significant improvements were observed on Trial 2 and 4, and numerical improvements were observed at Trials 1, 3 and 5.
- Solriamfetol 75 mg and 150 mg led to significantly more patients achieving improvements in their condition, as assessed using PGI-c and CGI-c, compared with placebo ($p<0.0001$ for solriamfetol 150 mg on PGI-c and CGI-c at all time-points ; $p<0.05$ for solriamfetol 75 mg on CGI-c and PGI-c at all time-points, except week 1 on CGI-c). Solriamfetol 37.5 mg showed numerical but not significant improvements compared with placebo at all time points.
- Solriamfetol dose-dependently increased FOSQ-10 scores at week 12, indicating improved ability to conduct daily activities, with significant results observed for the solriamfetol 150 mg dose (LS mean (SE) change from baseline was 3.0 (0.2), compared with 1.7 (0.2) for placebo; $p<0.05$).
- TONES 3 demonstrated the overall safety and tolerability profile of solriamfetol for treating EDS in OSA; the overall safety and tolerability was consistent with other clinical studies of solriamfetol in OSA.

TONES 5 (Long-term Phase 3 study)

- Results from the open-label phase of TONES 5 demonstrated that patients with OSA treated with solriamfetol (combined arm, including the unlicensed 300 mg dose) achieved clinically meaningful reductions in mean ESS from baseline[h] 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[h] to week 40 in Group A were [redacted] and [redacted] for the 75 and 150 mg doses, respectively. Mean changes from baseline[h] 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 5 dimension EuroQoL (EQ-5D-5L) and 36-item SF-36 version 2 (SF-36v2), were maintained during long-term open-label treatment with solriamfetol (combined arm).

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

- During the randomised withdrawal phase, after 6 months of open label treatment, patients with OSA who continued solriamfetol (including the unlicensed 300 mg dose) maintained their improved EDS status (based on ESS scores), as compared with patients who were switched to placebo and then experienced deterioration and worsening of EDS status (LS mean difference of [redacted] on ESS; [redacted]); absolute change in ESS was [redacted], [redacted] and [redacted], respectively for patients who were randomised to placebo, solriamfetol 75 mg or solriamfetol 150 mg .
- During the randomised withdrawal phase, ESS scores for patients receiving placebo worsened but not beyond baseline values, 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 any rebound hypersomnia. The safety and tolerability of long-term solriamfetol treatment were consistent with that observed in shorter-term clinical trials.

TONES 4 (Supportive Phase 3 study)

- The results observed in the randomised withdrawal phase of TONES 4 are consistent with those reported for TONES 5.
- During the randomised withdrawal phase (after 2 weeks of titration and 2 weeks of stable treatment), patients who were switched to placebo had significant worsening of their EDS (as demonstrated by increased ESS and reduced MWT scores), compared with patients who continued their stable dose of solriamfetol (LS mean difference between solriamfetol and placebo for MWT was 11.2 minutes; $p<0.0001$; and for ESS was -4.6; $p<0.0001$).
- Patients randomised to placebo also experienced objective and subjective worsening of their condition, as assessed using the CGI-c and PGI-c, compared with those who continued stable dose solriamfetol.
- A negative effect of withdrawal on patient QoL was observed, with patients randomised to placebo experiencing a reduction in FOSQ-10 scores over the 2 week withdrawal phase (LS mean difference favouring solriamfetol of 1.2; $p<0.05$).

Conclusions

- TONES 3, TONES 5, and TONES 4 have demonstrated the safety and efficacy of solriamfetol for treating EDS associated with OSA.
- Results were achieved across a range of subjective and objective outcome measures that were clinically meaningful, rapid in onset, lasted throughout the day, and maintained in the long-term (up to 52 weeks).
- Solriamfetol is well-tolerated and the AEs observed are consistent with a wake-promoting profile of effects expected.
- Reversal of treatment benefit upon discontinuation of solriamfetol treatment was observed without any related rebound hypersomnia.

B.2.3.1 Comparative summary of trial methodology

Three Phase 3 trials (TONES 3 and 5) and one supporting Phase 3 trial (TONES 4) provide evidence for solriamfetol for treating EDS in patients with OSA:

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

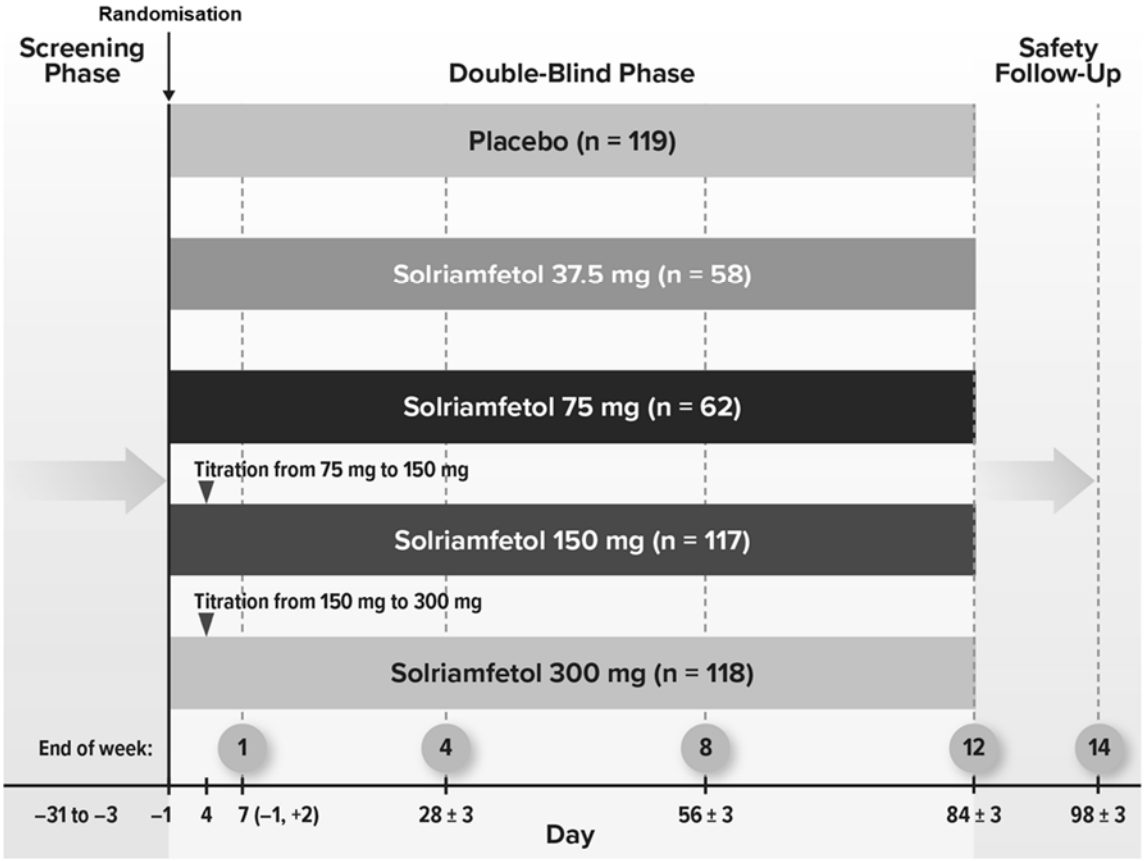
Trial design schematics are provided in Section B.2.3.1.1. The methodologies of these three trials are summarised in Section B.2.3.1.2. Trial endpoints and a description of each endpoint measure are provided in Section B.2.3.1.3.

B.2.3.1.1 Trial design

B.2.3.1.1.1 TONES 3 (Pivotal placebo-controlled trial)

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

Figure 2: TONES 3 study design (Safety Population)



Abbreviations: TONES, Treatment of Obstructive sleep apnoea and Narcolepsy Excessive Sleepiness.
Adapted from Weaver 2020 (100).

B.2.3.1.1.2 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 OSA or narcolepsy 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):

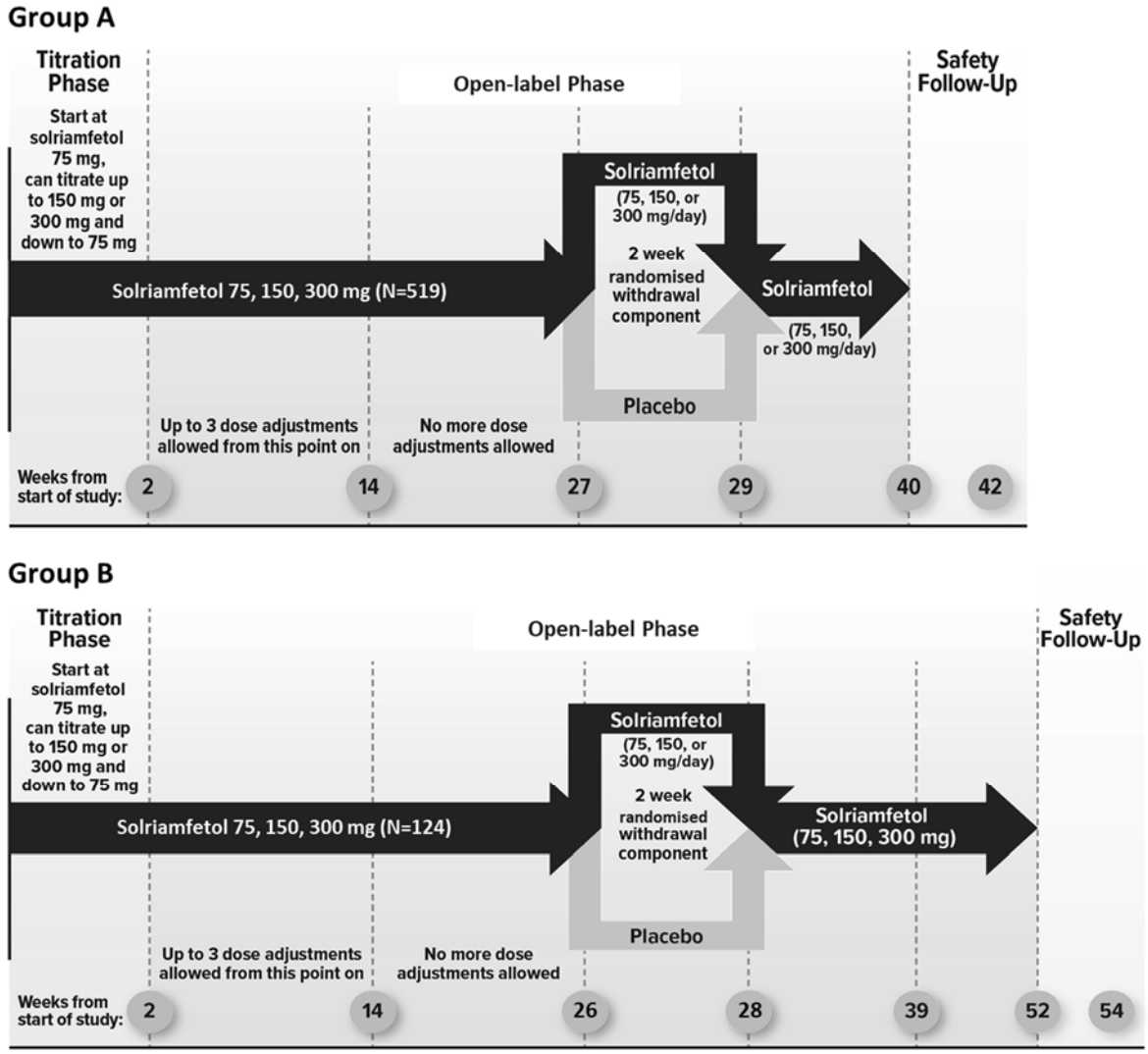
- Group A: patients who enrolled in TONES 5 immediately after completing the 12 week TONES 2 or TONES 3 Phase-3 studies, without a washout period/break in treatment between studies; these patients were planned for up to 40 weeks of treatment in TONES 5, to provide up to 52 weeks of continuous efficacy 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 solriamfetol treatment of unknown duration 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). Note that all patients were required to complete the titration phase of the study, [redacted].
- 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), 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. After the randomised withdrawal phase, all placebo-treated patients resumed the dose of solriamfetol that they were receiving prior to entering the randomised withdrawal for the remainder of the study (treatment resumed following 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 titrated back up to 150 mg per day thereafter) (Figure 3).

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.
Adapted from Malhotra 2019 (102).

B.2.3.1.1.3 TONES 4 (Supporting Phase 3 randomised withdrawal study)

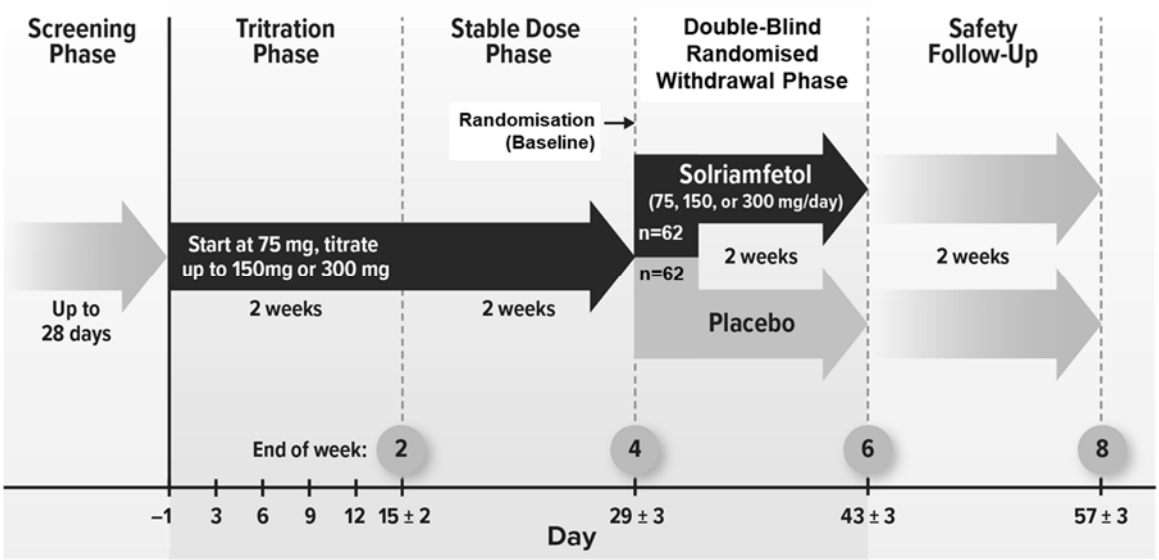
TONES 4 was a phase 3, multicentre, placebo-controlled, 2-arm parallel-group, 6-week double-blind, randomised-withdrawal study of safety and efficacy (Figure 4).

The study consisted of three phases:

- Titration phase (2 weeks), during which patients initiated open-label solriamfetol at the 75 mg dose, and were titrated to a maximum tolerated dose (maximum 300 mg).

- Stable-dose phase (2 weeks), during which patients continued to receive solriamfetol at the dose they were titrated to in the titration phase.
- Double-blind randomised phase (2 weeks), during which specific patients (Table 4 for criteria) were randomised to placebo or to continue their stable dose of solriamfetol.

Figure 4: TONES 4 study design (Safety Population)



Abbreviations: TONES, Treatment of Obstructive sleep apnoea and Narcolepsy Excessive Sleepiness.
Adapted from Strollo 2019 (105).

B.2.3.1.2 Description of trial methodologies for TONES 3–5

Table 4 outlines the trial methodology for the three Phase 3 trials of solriamfetol in patients with EDS and OSA (TONES 3–5). An explanation of each of the endpoints and how they are interpreted is provided in Table 6.

Table 4: Comparative summary of trial methodology

Trial no. (Acronym)	Study 14-003 (TONES 3)	Study 14-005 (TONES 5)	Study 14-004 (TONES 4)
Primary study objective	To evaluate the efficacy of solriamfetol administered qd for up to 12 weeks in doses of 37.5, 75, 150, and 300 mg (unlicensed) compared to placebo in the treatment of excessive sleepiness in adult patients with OSA.	**Open-label phase:** to evaluate the safety and tolerability of solriamfetol administered qd for up to 52 weeks in doses of 75, 150, and (unlicensed) 300 mg **Randomised withdrawal phase:** to evaluate the maintenance of efficacy of solriamfetol administered qd compared with placebo in adult patients with OSA or narcolepsy after ≥26 weeks.	To evaluate the efficacy of solriamfetol administered qd compared with placebo in the treatment of excessive sleepiness in adult patients with OSA
Secondary study objectives	To evaluate safety, tolerability and pharmacokinetics 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.	To evaluate the safety and tolerability of solriamfetol
Key eligibility criteria for participants	• Adults (18–75 years) with OSA diagnosed according to the ICSD-3 criteria and with current or prior use of a primary OSA therapy, including PAP, oral appliance or surgical intervention. • Baseline ESS score ≥10. • Mean baseline sleep latency <30 minutes on the first 4 of a 5-trial, 40-minute MWT.	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	• Adults (18–75 years) with OSA diagnosed according to the ICSD-3 criteria and with current or prior use of a primary OSA therapy, including PAP, oral appliance or surgical intervention. • Baseline ESS score ≥10 • Mean baseline sleep latency <30 minutes on the first 4 of a 5-trial, 40 minute MWT.

Trial no. (Acronym)	Study 14-003 (TONES 3)	Study 14-005 (TONES 5)	Study 14-004 (TONES 4)
	• Usual nightly sleep time ≥6 hours. Full eligibility criteria are provided in Appendix L.	was able to take solriamfetol for 40 weeks (Group A), or 52 weeks (Group B), and was able to complete all tests and visits described in the protocol. • Usual night sleep time ≥6 hours • Full eligibility criteria are in Appendix L.	• Usual night sleep time ≥6 hours Full eligibility criteria are provided in Appendix L.
Method of randomisation	• The investigator accessed an IVRS/IWRS to randomly assign patients to treatment. • Randomisation was stratified by compliance or non-compliance to primary OSA therapy. • Compliance was defined as history of a surgical intervention deemed effective in treating the airway obstruction, PAP use for ≥4 hours/night on ≥70% of nights, or historical report (with investigator concurrence) of oral appliance use on ≥70% of nights. • Non-compliance was defined as device use at a level lower than that specified above, no use of a device at all, **or** treatment with a surgical intervention deemed no longer effective (in the absence of compliant device use).	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 OSA or narcolepsy.	**Randomised-withdrawal phase (weeks 4–6)** • The investigator accessed an IVRS/IWRS to randomly assign patients to treatment. • Patients who completed the week 4 visit at the end of the stable-dose phase, and reported much/very much improvement on the PCI-c scale, and had numerical improvement in mean sleep latency on the MWT and in ESS score from the beginning of titration to week 4 were randomised 1:1 into the withdrawal phase. • Randomisation was stratified by compliance or noncompliance to primary OSA therapy at the end of the stable-dose phase. • Compliance to OSA therapy was defined as: PAP use ≥4 hours per night on ≥70% of nights, historical report of use of an oral appliance on ≥70% of nights, or receipt of an effective surgical intervention for OSA symptoms. • Non-compliance to primary OSA therapy was defined as usage of PAP or an oral appliance at a level that did not meet the

Trial no. (Acronym)	Study 14-003 (TONES 3)	Study 14-005 (TONES 5)	Study 14-004 (TONES 4)
			above criteria, or receipt of a surgical intervention for OSA that was no longer effective in the absence of compliant primary OSA therapy use.
Method of blinding (care provider, patient and outcome assessor)	• The study was conducted in a fully double-blind manner. All study drugs were prepared in identical opaque gelatin capsules to ensure adequate double-blinding, and all study personnel were blinded to the study treatments. • The master randomisation code was sequestered by the quality department at Jazz Pharmaceuticals and the code was not broken or released until all study data had been collected and accepted for analysis.	• 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.	• The titration and stable-dose phases of the study were not blinded. • A double-blind approach was used during the withdrawal phase, [redacted]. • [redacted].
Settings and locations where the data were collected	• 59 clinical sites in US, Canada, France, Germany, the Netherlands	• 79 clinical sites in North America and Europe	• [redacted] clinical sites in US, Finland France, Germany and Sweden
Trial drugs	Randomised 1:1:2:2:2 to receive treatment with identical opaque gelatin capsules: • Solriamfetol qd oral 37.5 mg • 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 mg and (unlicensed) 300 mg doses received 75 mg and 150 mg, respectively, on Days 1–3, with the full dose starting on Day 4. Patients	• [redacted] o [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).	• Titration phase: Patients started on 75 mg solriamfetol qd and were titrated up or down one level once every 3 days over 2 weeks to 75, 150 or (unlicensed) 300 mg solriamfetol. • Stable-dose phase: Patients continued at a stable dose for 2 weeks. • Double-blind randomised withdrawal phase: At week 4 patients were randomised 1:1 to receive placebo or continue their stable dose of solriamfetol.

Trial no. (Acronym)	Study 14-003 (TONES 3)	Study 14-005 (TONES 5)	Study 14-004 (TONES 4)
	randomised to other treatment groups did not undergo titration. Study drug was taken on an empty stomach within 1 hour of wakening.	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]	• Excluded medications varied by patient group (Group A or Group B) and included OTC or prescription medications that could affect evaluation of excessive sleepiness (Appendix L for details). • Patients with narcolepsy could have anti-cataplectic medications ([redacted] • [redacted]	• [redacted]

Trial no. (Acronym)	Study 14-003 (TONES 3)	Study 14-005 (TONES 5)	Study 14-004 (TONES 4)
Primary outcomes	See Section B.2.3.1.3		
Other outcomes used in the economic model/specified in the scope			
Pre-planned subgroups	• [redacted]	• [redacted]	• [redacted]

Abbreviations: ESS, Epworth Sleepiness Scale; ICSD-3, International Classification of Sleep Disorders-3; IVRS, Interactive Voice Response System; IWRS, Interactive Web Response System; MWT, Maintenance of Wakefulness Test; OSA, obstructive sleep apnoea; OTC, over the counter; PAP, positive airway pressure; qd, once daily; TONES, Treatment of Obstructive sleep apnoea and Narcolepsy Excessive Sleepiness; US, United States.

B.2.3.1.3 Trial outcomes

Trial endpoints for TONES 3, TONES 5 and TONES 4 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 3	TONES 5		TONES 4
		Open-label phase	Randomised-withdrawal phase	
Primary efficacy endpoint†	**Co-primary efficacy** • ESS: Change in ESS score, from baseline to week 12 • MWT: Change in mean sleep latency time (minutes), determined from first 4 trials of 40 minute MWT, from baseline to week 12.	• There was no primary efficacy endpoint during the open-label phase.	• **ESS**: Change from the beginning to the end of the randomised withdrawal phase.	**Co-primary efficacy** • ESS: Change in ESS from the end of the stable-dose phase (week 4) to the end of the withdrawal phase (week 6) • MWT: Change in mean sleep latency time (minutes), using the first 4 trials of 40 minute MWT, from the beginning (week 4) to the end of the withdrawal phase (week 6).
Other outcomes used in economic model and/or specified in scope†	**Secondary efficacy** • ESS: Change in ESS score from baseline to weeks 1, 4 and 8. • MWT: Change in mean sleep latency time (minutes), determined from first 4 trials of a 40-minute MWT from baseline to week 1 and 4. • Time course of efficacy on MWT: Change in sleep latency time (minutes) on each of five MWT trials, at week 12.	**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	**HRQoL (secondary efficacy/exploratory):** • FOSQ 10 subscale and total scores. **Safety** • Including AEs, serious AEs, discontinuations.

	TONES 3	TONES 5		TONES 4
		Open-label phase	Randomised-withdrawal phase	
	Post-hoc analyses • ESS: percentage of patients with normal ESS scores (ESA ≤10; Table 6) at week 12. • ESS and MWT: Estimates of effect sizes of the change from baseline to week 12 based on LS mean divided by SD (Cohen's d). • MWT: percentage of patients with MWT sleep latency ≥20 minutes, based on a value of 19.4 minutes reported as the lower limit of normal and incorporated into the AASM practice parameters (Table 6). **Exploratory:** • PSG parameters: including total sleep time, number of awakenings, and wake after sleep onset at week 12. **HRQoL** • FOSQ-10 total scores. • SF-36v2 domain, mental and physical component, and total scores. • EQ-5D-5L dimensions, VAS and index values. **Safety** • Including AEs, serious AEs, discontinuations.	**HRQoL endpoints:** • [redacted]. **Safety** • Including AEs, serious AEs, discontinuations.		

	TONES 3	TONES 5		TONES 4
		Open-label phase	Randomised-withdrawal phase	
All other reported outcomes	**Key secondary efficacy** • PGI-c: percentage of patients reported as improved‡ at week 12. **Secondary efficacy** • PGI-c: percentage of patients reported as improved‡ at weeks 1, 4 and 8. • CGI-c: percentage of patients reported as improved‡ at weeks 12, 8, 4 and 1. **Productivity** • WPAI:SHP scores. **Exploratory** • Change in frequency of primary OSA therapy.	**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.	**Key secondary efficacy** • PGI-c: percentage of patients reported as worse§ after the withdrawal phase (week 6). **Secondary efficacy** • CGI-c: percentage of patients reported as worse§ after the withdrawal phase (week 6). **Exploratory** • [redacted].

Abbreviations: AASM, American Academy of Sleep Medicine; AE, adverse event; CGI-c; Clinical Global Impression of change; EQ-5D-5L, 5-level 5-dimension EuroQoL; 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; VAS, visual analogue scale; WPAI:SHP, Work Productivity and Activity Impairment Questionnaire: Specific Health Problem V2.0.

† Outcomes in bold are incorporated in the health economic model.

‡ Improvement on PGI-c and CGI-c defined as “very much”, “much”, or “minimally” improved.

§ Worsening on PGI-c and CGI-c defined as “minimally”, “much”, or “very much” worse.

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 (107, 108), and provides a measure of a person's general level of daytime sleepiness or their average sleep propensity in daily life (108). • 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 (108), where higher scores represent more severe sleepiness. • ESS scores ≤10 are considered within the normal range (107-109). • Mean (range) scores in people with excessive sleepiness due to OSA are 11.7 ± 4.6 (4–23) (108). • 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) (110-112). • **TONES 3–5:** Patients were asked to complete the ESS with regard to the level of sleepiness they experienced over the previous [redacted].
MWT sleep latency	• The MWT provides a validated objective assessment of the ability to remain awake (wakefulness) (113-115). • 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 (115). • 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 (115). • 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 (115), with 19.4 minutes reported as the lower limit of normal (114). • **TONES 3/4:** MWT evaluations were performed subsequent to an overnight stay at the study site for nocturnal PSG using a standard protocol. • **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 (98). • Worsening defined as ratings of "minimally", "much", "very much" worse (105).
CGI-c	• On the CGI-c, investigators rate their impression of any change in the patient's condition from when they started treatment (scores ranging from 1=very much improved to 7=very much worse) (98). • Improvement was defined as ratings of "very much", "much", or "minimally" improved (98). • Worsening defined as ratings of "minimally", "much", "very much" worse (105).

	• Baseline scores were assessed using the CGI-s, for which investigators rated their impression of the patient's symptom severity.
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 (116). • Functional status is assessed through 5 subscales (activity level, general productivity, social outcome, intimacy and sexual relationships, and vigilance) and a total score (116). • 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 (116). • 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 (117). • 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) (117).
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) (118). • 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") (118).

WPAI:SHP	• The WPAI:SHP questionnaire is a 6-item patient-reported questionnaire that measures percentage of: work time missed (absenteeism), impairment while working (presenteeism), overall work impairment (work impairment), and activity impairment (activity impairment) because of a specified health problem during the past 7 days (119, 120).
	• The validity of the WPAI has been established in a number of diseases (121).
	• Outcomes are expressed as impairment percentages, with higher numbers indicating greater impairment and less productivity (119). A negative change from baseline represents improvement.
	• In TONES studies
	  • **TONES 3:** The WPAI:SHP was used with "OSA" as the specified health problem.
	  • **TONES 5**: The WPAI:SHP was used with "OSA" or "narcolepsy" as the specified health problem.
	  • **TONES 4:** WPAI:SHP was not used.

Abbreviations: AASM, American Academy of Sleep Medicine; CGI-c; Clinical Global Impression of change; CGI-s; Clinical Global Impression of symptom severity; EDS, excessive daytime sleepiness; EQ-5D-5L, 5-level 5-dimension EuroQoL; 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 3 (Pivotal placebo-controlled trial)

A total of 474 patients were randomised and took at least one dose of study drug, forming the Safety Population. Baseline demographic and clinical characteristics were similar across treatment arms (Table 7):

- The majority of patients were white, male, with mean body mass index (BMI) greater than 30 kg/m^2.
- Approximately 90% of patients were rated as at least moderately ill by investigators as assessed by the Clinical Global Impression of Severity (CGI-s) (43% moderately ill; 32% markedly ill; 13% severely ill; 2% among the most extremely ill).
- Baseline sleep latency, as measured using the MWT, and demonstrating ability to stay awake, ranged between 12.0 and 13.6 minutes. Baseline mean ESS scores ranged between 14.8 and 15.6.

B.2.3.2.1.1 Primary OSA therapy

Of the Safety Population at baseline, 69.7% of patients on placebo and 73.5% of patients on solriamfetol self-reported (with clinician concurrence) current or prior use of a primary OSA therapy (prior use of primary OSA therapy was defined as ≥4 weeks of usage with ≥1 documented adjustment [e.g., different mask, pressure, or modality]). Of the patients with current or prior use of a primary OSA therapy:

- A history of a surgical intervention for OSA was reported in 17.6% and 13.5% of patients on placebo and solriamfetol, respectively
- 91.6% of the placebo and 92.7% of the solriamfetol group were using PAP
- 2.4% of the placebo and 1.1% of the solriamfetol group were using another type of device,
- 6.0% of the placebo and 6.1% of the solriamfetol did not specify the type of device.

Table 7: TONES 3: Baseline demographics and clinical characteristics (Safety Population)

Characteristic†	Placebo N=119	Solriamfetol			
		37.5 mg N=58	75 mg N=62	150 mg N=117	300 mg (unlicensed) N=118
Age, years	54.1 (11.4)	57.1 (10.2)	54.4 (11.5)	52.7 (10.6)	53.2 (10.6)
Male, n (%)	77 (64.7)	39 (67.2)	35 (56.5)	72 (61.5)	74 (62.7)
Race, n (%)					
White	87 (73.1)	45 (77.6)	46 (74.2)	93 (79.5)	90 (76.3)
Black or African American	26 (21.8)	10 (17.2)	14 (22.6)	18 (15.4)	21 (17.8)
Asian	4 (3.4)	3 (5.2)	1 (1.6)	3 (2.6)	6 (5.1)
Other	2 (1.6)	0	1 (1.6)	3 (2.6)	1 (0.8)
Body mass index, kg/m^2	33.1 (5.2)	34.1 (5.3)	33.4 (5.7)	33.3 (4.8)	32.9 (5.6)
Mean sleep latency (MWT), minutes	12.4 (7.2)	13.6 (8.1)	13.1 (7.2)	12.5 (7.2)	12.0 (7.3)
AHI, median (IQR)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ESS score					
Mean (SD)	15.6 (3.3)	15.1 (3.5)	14.8 (3.5)	15.1 (3.4)	15.2 (3.1)
Median (IQR)	15 (10, 24)	15 (10, 24)	15 (10, 23)	15 (10, 24)	15 (10, 23)
CGI-s, n (%)					
1=Normal, not at all ill	0	0	0	0	0
2=Borderline ill	3 (2.5)	1 (1.7)	1 (1.6)	2 (1.7)	1 (0.8)
3=Mildly ill	8 (6.7)	5 (8.6)	4 (6.5)	7 (6.0)	10 (8.5)
4=Moderately ill	48 (40.3)	28 (48.3)	31 (50.0)	53 (45.3)	44 (37.3)
5=Markedly ill	39 (32.8)	14 (24.1)	15 (24.2)	41 (35.0)	44 (37.3)
6=Severely ill	15 (12.6)	9 (15.5)	7 (11.3)	14 (12.0)	17 (14.4)
7=Among the most extremely ill	4 (3.4)	1 (1.7)	3 (4.8)	0	2 (1.7)
Missing	2 (1.7)	0	1 (1.6)	0	0
Primary OSA therapy compliance‡, n (%)					
Compliant	83 (69.7)	40 (69.0)	45 (72.6)	80 (68.4)	86 (72.9)
Non-compliant	36 (30.3)	18 (31.0)	17 (27.4)	37 (31.6)	32 (27.1)

Abbreviations: AHI, apnoea hypopnoea index; CGI-s, Clinical Global Impression of severity; 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.
† Data are presented as mean (SD) unless otherwise noted.
‡ Includes patients using a primary OSA therapy at baseline; see Table 4 for definition of compliance.
Source: CSR Table 14.2.13.1 (97); Schweitzer 2019 (98).

B.2.3.2.2 TONES 5 (Long-term Phase 3 study)

This submission pertains to solriamfetol for treating EDS due to OSA, and only baseline characteristics for the OSA population are presented. Baseline characteristics for the overall population are presented in Appendix L. Baseline characteristics for the patients with narcolepsy are not presented herein but were presented in the appraisal of solriamfetol for treating EDS caused by narcolepsy (ID1602).

B.2.3.2.2.1 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 OSA in TONES 5 are presented in Table 8.

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

- The majority of patients were white (77.9%), male (61.6%), with mean BMI greater than 33 kg/m^2.
- Approximately [redacted]% were rated by investigators as being at least moderately ill.
- Compliance to primary OSA therapy was 77.7%.
- Baseline[i] mean ESS score at the beginning of this study was 15.2 for Group A and 15.0 for Group B.

Table 8. TONES 5: Baseline demographics and clinical characteristics of patients with OSA[†] (Safety Population)

Characteristic[‡]	Combined solriamfetol OSA N=417
Age, years	55.1 (10.7)
Male, n (%)	257 (61.6)
Race, n (%)	
White	325 (77.9)
Black or African American	[redacted]
Other	[redacted]

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

Characteristic‡	Combined solriamfetol OSA N=417
Body mass index, kg/m^2	33.5 (5.1)
Baseline ESS score‖	15.2 [redacted]
Baseline ESS score§	15.0 [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	138 (33.1)
6=Severely ill	58 (13.9)
7=Among the most extremely ill	[redacted]
Missing	[redacted]
Compliant to primary OSA therapy§§, n (%)	324 (77.7)

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 OSA; therefore results for narcolepsy are not presented.
‡ Data are presented as mean (SD) unless otherwise noted.
‖ Baseline score in the parent study (Group A only).
§ Baseline score in the current study (Group B only).
§§ See Table 4 for definition of compliance.
Source: Schweitzer 2019 (98); Weaver 2020 (100); CSR Table 9 and Table 10 (101).

B.2.3.2.2.2 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 patients in the randomised withdrawal phase, baseline disease characteristics were generally similar to the Safety Population of the open-label period.

B.2.3.2.3 TONES 4 (Supporting Phase 3 randomised withdrawal study)

A total of 174 patients took at least one dose of solriamfetol during the titration phase, representing the overall Safety Population. A total of 124 patients were randomised into the withdrawal phase and comprised the Safety Population for that phase. Baseline demographics and clinical characteristics of the withdrawal phase Safety Population were similar across phases and between groups (Table 9).

For the overall Safety Population (start of titration phase): The majority of patients were white (78.7%), male (61.5%), with mean BMI greater than 33 kg/m^2.

- Approximately 85% were rated by investigators as being at least moderately ill
- Compliance (Table 4 for definition) to primary OSA therapy was 71.3%.
- Baseline sleep latency (ability to stay awake) as measured using the MWT was 13.2 minutes. Baseline mean ESS scores was 15.4.

Table 9: TONES 4: Baseline demographics and clinical characteristics (Safety Population)

	Titration Phase	Stable-dose phase	Double Blind Withdrawal Phase	
Characteristic†	**Combined solriamfetol N=174**	**Combined solriamfetol N=157**	**Placebo N=62**	**Combined solriamfetol N=62**
Age, years	54.8 (10.5)	55.4 (10.2)	56.2 (9.8)	56.3 (11.4)
Male, n (%)	107 (61.5)	97 (61.8)	41 (66.1)	36 (58.1)
Race, n (%)				
White	137 (78.7)	121 (77.1)	45 (72.6)	50 (80.6)
Black or African American	34 (19.5)	34 (21.7)	15 (24.2)	12 (19.4)
Other	3 (1.7)	2 (1.3)	2 (3.2)	0
Body mass index, kg/m^2	33.3 (5.4)	33.3 (5.2)	33.3 (5.5)	32.9 (5.0)
Mean sleep latency (MWT, min)	13.2 (7.5)	12.9 (7.1)	12.3 (7.9)	13.0 (6.7)
ESS score	15.4 (3.4)	15.5 (3.5)	16.0 (3.5)	15.3 (3.5)
CGI-s, n (%)				
1=Normal, not at all ill	0	0	0	0
2=Borderline ill	6 (3.4)	6 (3.8)	3 (4.8)	2 (3.2)
3=Mildly ill	21 (12.1)	18 (11.5)	7 (11.3)	6 (9.7)
4=Moderately ill	71 (40.8)	61 (38.9)	23 (37.1)	23 (37.1)
5=Markedly ill	43 (24.7)	41 (26.1)	15 (24.2)	20 (32.3)
6=Severely ill	28 (16.1)	26 (16.6)	11 (17.7)	10 (16.1)
7=Among the most extremely ill	5 (2.9)	5 (3.2)	3 (4.8)	1 (1.6)
Missing	0	0	0	0
Compliant to primary OSA therapy‡, n (%)	124 (71.3)	119 (75.8)	47 (75.8)	49 (79.0)

Abbreviations: CGI-s, Clinical Global Impression of severity; 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.
† Data are presented as mean (SD) unless otherwise noted.
‡ See Table 4 for definition of compliance.
Source: Strollo 2019 (105).

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 3, TONES 5 and TONES 4 trials are defined in Table 10. The number of patients in each population set for each trial is provided in Appendix D.

Table 10: Analysis sets used in TONES trials

	TONES 3	TONES 5	TONES 4
Safety Population	• All patients received ≥1 dose of study drug. • [redacted]	• All patients who received ≥1 dose of study drug. • [redacted]	• All patients received ≥1 dose of study drug. • [redacted].
mITT Population	• All patients who received ≥1 dose of study drug and had baseline and ≥1 post-baseline evaluation of MWT or ESS. • Used for co-primary endpoints and other efficacy endpoints.	• 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.	• All patients who were randomised into the withdrawal phase, received ≥1 dose of study drug, and had a week 4 and ≥1 post-week 4 assessment of MWT or ESS. • Used for co-primary endpoints and other efficacy endpoints.
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 trials are presented in Table 11.

Table 11: Summary of statistical analyses

Trial number (acronym)	TONES 3	TONES 5	TONES 4
Hypothesis objective	• To evaluate the efficacy of solriamfetol administered qd for up to 12 weeks in doses of 37.5, 75, 150, and (unlicensed) 300 mg compared to placebo in the treatment of excessive sleepiness in adult patients with OSA.	Primary null hypothesis: • [redacted] Secondary null hypotheses: • [redacted] • [redacted]	• To evaluate the efficacy of solriamfetol administered qd compared with placebo in the treatment of excessive sleepiness in adult patients with OSA.
Sample size, power calculation	• Approximately 440 patients were planned for enrolment with approximately 55 patients in the solriamfetol 37.5 and 75 mg groups, and approximately 110 patients in the placebo and solriamfetol 150 and (unlicensed) 300 mg groups. • A sample size of 99 patients per group (placebo, 150 mg, and [unlicensed] 300 mg) was estimated to provide at least	• [redacted] • [redacted]	• Approximately 200 patients were planned for enrolment to ensure ≥122 patients were randomised in the withdrawal phase. • A sample size of 61 patients per group (placebo, solriamfetol) was estimated to provide at least 90% power to detect a difference between the placebo and solriamfetol groups in the change from the beginning to the end of the withdrawal

Trial number (acronym)	TONES 3	TONES 5	TONES 4
	90% power to detect a difference between placebo and the 150 mg and (unlicensed) 300 mg groups in the change from baseline to week 12 of 5 minutes in the mean sleep latency on the MWT and 3.5 points on the ESS. This calculation was informed by TONES 1 (122)‡ and used common SDs for the change from baseline of 10 minutes on the MWT and 6 points on the ESS, and a 2-sided significance level of 0.05 using a t-test. • The two lower dose arms were not powered for statistical significance but were included to adequately characterise the minimal effective dose.	• A sample size of 300 patients in the withdrawal phase (~150 per group) was estimated to provide at least 95% power to detect a difference of 3 points in ESS 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.	phase of 6 minutes in MWT mean sleep latency and 3.5 points in the ESS. This calculation assumed common SDs for the change during the withdrawal phase of 9.5 minutes on the MWT and 5 points on the ESS, and a 2-sided significance level of 0.05 using a t-test.
Significance levels and multiplicity	• To address the multiplicity issue due to multiple efficacy endpoints and doses, a fixed hierarchical testing sequence was employed, starting with the highest solriamfetol dose for the co-primary endpoints (MWT, ESS both at week 12) and the key secondary endpoint (PGI-c at week 12), with testing proceeding to each subsequent lower dose if statistical significance was met. • [redacted]	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	• To address the multiplicity issue due to multiple efficacy endpoints, a fixed hierarchical testing sequence was employed, starting with comparison of combined solriamfetol vs placebo for the co-primary efficacy endpoints MWT and ESS, followed by PGI-c if both co-primary endpoints were significant. • [redacted]

Trial number (acronym)	TONES 3	TONES 5	TONES 4
	[redacted]. • Analyses were conducted at the 2-sided significance level of 0.05; for analyses that were not part of the prespecified hierarchical analysis, no multiplicity adjustments were employed and p-values presented are considered nominal.	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: • Evaluated using a MMRM model, with fixed effects for treatment, time, treatment-by-time interaction, stratification factor (compliant or non-compliant to OSA therapy), and baseline value of the efficacy endpoint; results are presented as LS mean (SE) change from baseline. Co-primary sensitivity/secondary analyses: • [redacted] • [redacted] Secondary/other endpoints: • PGI-c, CGI-c and EQ-5D-5L Dimensions endpoints were evaluated using a	Withdrawal phase • Primary endpoints primary analyses: • Evaluated using ANCOVA, [redacted]. • Results are presented as LS mean (95% CI) treatment difference. • Secondary/other endpoints: • PGI-c and CGI-c were evaluated using a chi-squared test. • [redacted] Open label phase • [redacted]	Co-primary endpoints primary analyses: • Evaluated using ANCOVA, with fixed effects for treatment group, measurement at week 4, and random assignment stratification factor (primary OSA therapy compliant or non-compliant). • Results are presented as LS mean (95% CI) treatment difference vs placebo . Co-primary endpoints sensitivity/secondary analyses: • [redacted] • Secondary analyses were conducted using the same statistical method as the primary analysis but based on the Per-Protocol Population. Secondary/other endpoints: • PGI-c and CGI-c were evaluated using a

Trial number (acronym)	TONES 3	TONES 5	TONES 4
	chi-square test. • For other MWT and ESS endpoints and the FOSQ-10, SF-36v2, EQ VAS, EQ-5D-5L Index, and WPAI:SHP endpoints, an MMRM model was used.	[redacted] Sensitivity/Secondary analyses • [redacted] • [redacted] • [redacted]	chi-square test. • For FOSQ-10 endpoints, [redacted]
Data management, patient withdrawals	Co-primary endpoints • For primary analysis of the primary endpoints missing data were evaluated using MMRM. [redacted] (“Statistical analysis” in this table). Other endpoints • [redacted]	Primary and secondary endpoints • [redacted] • [redacted]	Co-primary endpoints • The LOCF approach was used to account for patients who discontinued early in the withdrawal phase. • Sensitivity analyses using single and multiple imputation methods were also conducted (“Statistical analysis” in this table). Other endpoints

Trial number (acronym)	TONES 3	TONES 5	TONES 4
	[redacted] • As described under "statistical analysis" in this table, other MWT and ESS endpoints and the FOSQ-10, SF-36v2, EQ VAS, EQ-5D-5L Index, and WPAI:SHP endpoints, were analysed using MMRM. Post-hoc analyses • Assessment of the percentage of patients achieving normal values on the MWT and ESS were conducted for 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.	• [redacted]

Abbreviations: ANCOVA, analysis of covariance; CGI-c; Clinical Global Impression of change; CI, confidence interval; EQ-5D-5L, 5-level 5-dimension EuroQoL; 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
‡ Phase 2b, 12-week study of solriamfetol in patients with narcolepsy.

B.2.4.3 Participant flow in the relevant randomised controlled trials

For full details of participant flow for the TONES 3, TONES 5, and TONES 4 trials, see Appendix D. Summaries for each trial are provided in the subsequent sections.

B.2.4.3.1 TONES 3 (Pivotal placebo-controlled trial)

- In total, 984 patients were screened for entry into the study, with 508 screen failures.
- 476 patients were randomly assigned to receive solriamfetol 37.5 mg (n=59), solriamfetol 75 mg (n=61), solriamfetol 150 mg (n=118), solriamfetol 300 mg (n=119), or placebo (n=119).
- 474 patients were randomised and took at least one dose of study drug (Safety Population).
- 459 patients successfully completed at least one post-baseline evaluation of MWT or ESS (modified intent-to-treat [mITT] Population).
- Adverse events were the most common reason overall for withdrawal (n=24, 5.2%; mITT Population).
- Overall, 404 patients completed the study.

B.2.4.3.2 TONES 5 (Long-term Phase 3 study)

- 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=417 OSA; n=226 narcolepsy).
    - ◊ 519 patients (81%) were from Group A and had completed the TONES 2 or TONES 3 pivotal trials for solriamfetol in OSA or narcolepsy, 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] OSA: [redacted] placebo, [redacted] solriamfetol]; [redacted] narcolepsy [redacted] placebo, [redacted] solriamfetol]).
- Overall, 458 patients completed the study (n=308 OSA; n=150 narcolepsy).
  - Of the 185 patients who discontinued, the most frequently reported reasons were AEs (9.5%: [OSA, 9.1%; narcolepsy, 10.2%]), and lack of efficacy (8.4% [OSA, 3.6%; narcolepsy, 17.3%]).

B.2.4.3.3 TONES 4 (Supporting Phase 3 randomised withdrawal study)

- In total, 402 patients were screened for entry into the study, with 228 screen failures.
- 174 patients were enrolled and received solriamfetol during the titration phase (Safety Population).
  - During the titration phase 17 patients discontinued; the most common reason (n=7, 4.0%) was MWT criteria not met.
- 157 patients continued into the stable-dose phase: solriamfetol 75 mg (n=23, 14.6%), solriamfetol 150 mg (n=50, 31.8%), solriamfetol 300 mg (n=84, 53.5%).
  - Nine patients discontinued during the stable-dose phase with ‘lost to follow-up’ and ‘consent withdrawn’ being the most common reasons for discontinuation (n=3; 1.9% for both).
  - Twenty-four patients completed the stable-dose phase but did not continue to the withdrawal phase; failure to meet the randomisation criteria was the most common reason (n=21, 13%).

- 124 patients entered the randomised withdrawal phase and were assigned 1:1 to receive placebo (n=62) or solriamfetol (n=62) at the dose taken in the stable-dose phase: n=9 (14.5%), n=26 (41.9%), and n=27 (43.5%) received solriamfetol 75 mg, 150 mg, and 300 mg, respectively.
- 122 patients who were randomised into the withdrawal phase and who successfully completed a week 4 and ≥1 post-week 4 evaluation of MWT or ESS (mITT Population).
- Overall, 122 patients completed the study.

B.2.5 Quality assessment of the relevant clinical effectiveness evidence

In accordance with the NICE recommended checklist for RCT assessment of bias, a summarised quality assessment for the pivotal trial TONES 3 and the supporting trial TONES 4 is provided below. A tabulated summary quality assessment for TONES 3 and TONES 4 is provided in Table 12, and a tabulated full quality assessment is provided in Appendix D, Table 5.

A summarised quality assessment for the non-RCT trial TONES 5 is provided below. TONES 5 was originally designed as a non-randomised, long-term, single arm study, and because only a proportion of patients entered the 2-week randomised withdrawal phase, a non-RCT checklist was used for quality assessment; the tabulated full quality assessment for TONES 5 is provided in Appendix D, Table 6.

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

TONES 3 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. The risk of bias in TONES 3 was low.

TONES 4 (Supporting Phase 3 randomised withdrawal study)

TONES 4 was a Phase 3 study with a double-blind, placebo-controlled, randomised withdrawal phase to evaluate the effect of abrupt solriamfetol withdrawal. The randomised withdrawal phase was conducted in a double-blind manner, with patients, investigators and study personnel blinded to study drug treatments. TONES 4 is a supporting RCT to the non-RCT TONES 5, and the results of the randomised withdrawal phase for TONES 4 are consistent with those in TONES 5.

Table 12: Quality assessment results for parallel group RCTs

Trial number (acronym)	15-003 (TONES 3)	15-004 (TONES 4)
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 ITT 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)?	No	No

Abbreviations: ITT, intention-to-treat.

TONES 5 (Long-term Phase 3 study)

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. The study was conducted in accordance with Good Clinical Practice, and with the Standard Operating

Procedures of the contract research organisation 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 3 (Pivotal placebo-controlled trial)

Results for the unlicensed 300 mg dose have not been presented.

B.2.6.1.1 Treatment exposure in TONES 3

The mean duration of treatment exposure was generally comparable across the placebo and solriamfetol groups, ranging from [redacted] days. The median exposure was [redacted] days for all groups.

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

The co-primary endpoints of change from baseline at week 12 in ESS and MWT were met at all solriamfetol doses.

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

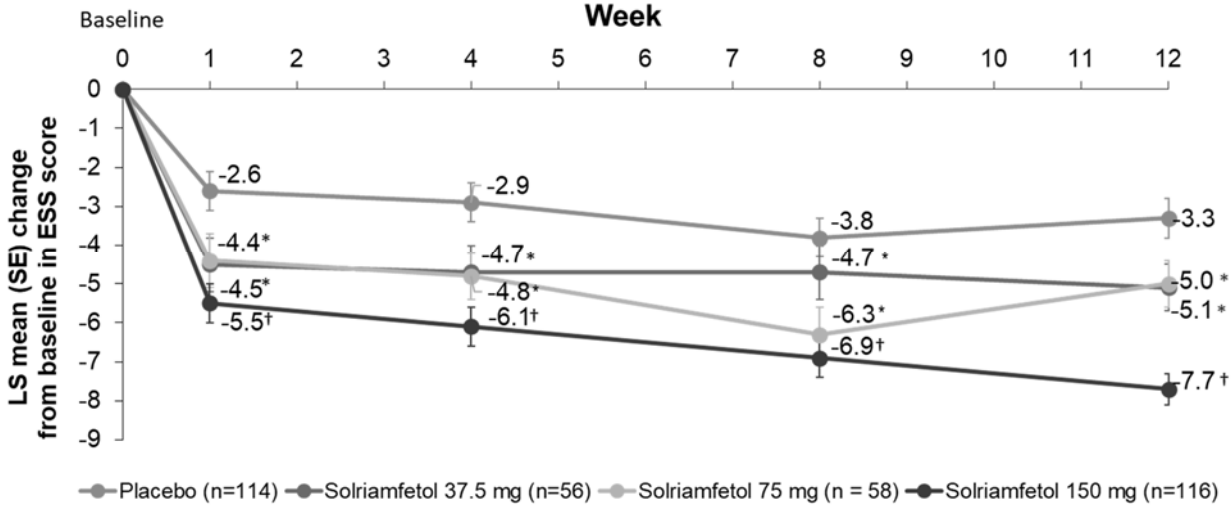
- Statistically significant improvement in ESS scores compared with placebo for all doses of solriamfetol (Table 13, Figure 6).
- Statistically significant improvement in 12-week MWT mean sleep latency times compared with baseline for all solriamfetol doses (Figure 5).

Table 13: TONES 3: Co-primary and key secondary efficacy endpoints (week 12; mITT Population)

	Placebo N=114	Solriamfetol 37.5 mg N=56	Solriamfetol 75 mg N=58	Solriamfetol 150 mg N=116
Primary endpoints				
Change in ESS score from baseline to week 12				
LS mean (SE)	−3.3 ([redacted]	−5.1 [redacted]	−5.0 [redacted]	−7.7 [redacted]
LS mean difference vs. placebo		−1.9	−1.7	−4.5
95% CI		−3.4 to −0.3	−3.2 to −0.2	−5.7 to −3.2
p value†		0.0161	0.0233	<0.0001
Change in MWT from baseline to week 12, minutes				
LS mean (SE)	0.2 [redacted]	4.7 [redacted]	9.1 [redacted]	11.0 [redacted]
LS mean difference vs. placebo		4.5	8.9	10.7
95% CI		1.2 to 7.9	5.6 to 12.1	8.1 to 13.4
p value†		0.0086	<0.0001	<0.0001
Key secondary endpoint				
Patients reported improvement (minimally, much, or very much) on PGI-c at week 12				
Yes, n (%)	56 (49.1)	31 (55.4)	42 (72.4)	104 (89.7)
Difference [yes] from placebo, % (95% CI)		6.2 (-9.7 to 22.2)	23.3 (8.6 to 38.0)	40.5 (29.8 to 51.3)
p value‡		0.4447	0.0035	<0.0001

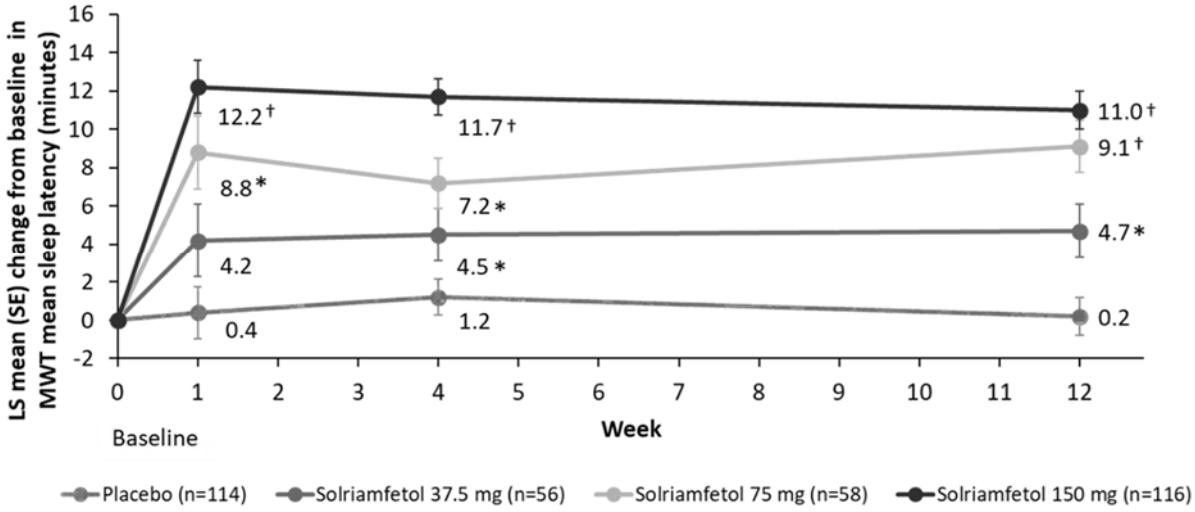
Abbreviations: CI, confidence interval; CSR, clinical study report; ESS, Epworth Sleepiness Scale; LS, least squares; mITT, modified intent to treat; MMRM, mixed effects repeated measures; MWT, Maintenance of Wakefulness Test; PGI-c, Patient Global Impression of change; SE, standard error; TONES, Treatment of Obstructive sleep apnoea and Narcolepsy Excessive Sleepiness.
†p values for MWT and ESS based on MMRM model with change from baseline as the response variable and fixed effect for treatment, visit, treatment by visit, randomization factor, and covariate of baseline value.
‡p value for PGI-c based on a chi-square test;
[redacted].
Source: Schweitzer 2019 (98); CSR Table 13 (97); Weaver 2020 (100).

Figure 5: TONES 3: 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. MMRM model with change from baseline as response variable and fixed effect of treatment, visit, treatment by visit, randomisation factor and covariate of baseline value.
Source: Schweitzer 2019 (98); CSR Table 14.2.2.2.1 (97); Weaver 2020 (100).

Figure 6: TONES 3: 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. MMRM model with change from baseline as response variable and fixed effect of treatment, visit, treatment by visit, randomisation factor and covariate of baseline value.
Source: Schweitzer 2019 (98); CSR Table 14.2.1.2.1 (97); Weaver 2020 (100).

B.2.6.1.3 Secondary analysis of co-primary endpoints

[redacted] (ESS and MWT):

- 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.
  [redacted]
- [redacted] (mITT Population).

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

- A statistically significant improvement compared with placebo was observed from baseline to week 12 for the key secondary endpoint of PGI-c (representing subjective improvements in their condition) for all solriamfetol doses, except the 37.5 mg dose (Table 13).
- Of patients on solriamfetol 75, and 150 mg, respectively 72.4% ($p<0.05$) and 89.7% ($p<0.0001$) reported overall improvement on the PGI-c, compared with placebo (49.1%).

B.2.6.1.5 Secondary endpoints: ESS

B.2.6.1.5.1 ESS over the study period

- Statistically significant dose-dependent decreases were observed in ESS score, indicating reduced sleepiness compared with placebo; these decreases were observed as early as week 1 (the first point of measurement in the study) and remained stable over 12 weeks of treatment (Figure 5).
- The decreases were significantly greater for all doses of solriamfetol compared with placebo at all time points ($p<0.05$), except the 37.5 mg dose at week 8.
- Improvements on the ESS compared with placebo for solriamfetol 150 mg were >3 points [redacted] at weeks 1, 4 and 8, and >4 points at week 12 ($p<0.0001$) (Table 13), representing a clinically meaningful improvement in EDS over placebo (based on an MCID of 2–3 points (110)).

B.2.6.1.5.2 ESS effect sizes (Post-hoc analysis)

- At week 12, effect sizes (Cohen's d) were 0.4, 0.4, and 1.0 for solriamfetol 37.5, 75, and 150 mg, respectively.

B.2.6.1.5.3 Patients achieving normal ESS scores (post-hoc analysis)

- ESS scores ≤10 are considered within the normal range (107, 108).
- At baseline, 5.4%, 5.2%, and 7.8% of patients receiving solriamfetol 37.5, 75 and 150 mg respectively, had ESS scores ≤10 compared with 4.4% of placebo patients.
- At week 12, solriamfetol dose-dependently increased the percentage of patients with normal ESS scores (ESS ≤10) to 51.8%, 55.2% and 70.7% for solriamfetol 37.5, 75 and 150 mg, respectively, at week 12, compared with 37.7% at week 12 in the placebo group, demonstrating the clinical relevance of solriamfetol in reducing EDS in patients with OSA.

B.2.6.1.6 Secondary endpoints: MWT

B.2.6.1.6.1 MWT over the study period

- Dose-dependent improvements from baseline in MWT sleep latency were observed as early as week 1 (the first point of measurement in the study) post-treatment initiation and ranged from 4.2 to 12.2 minutes for the 37.5 to 150 mg doses of solriamfetol compared with placebo (0.4 minutes); the effects on MWT were statistically significant for the solriamfetol 75 mg ($p<0.05$) and 150 mg ($p<0.001$) doses from week 1.
- Improvements in MWT were maintained from week 1 across the 12 weeks of the study for all solriamfetol doses (37.5, 75, 150 mg), with all three doses having statistically significant improvements compared with placebo at weeks 4 and 12 (all $p<0.05$) (Figure 6).
- The LS mean change from baseline exceeded 10 minutes at all time points with solriamfetol 150 mg (11.0–12.2 minutes), versus placebo (0.2-1.2 minutes).

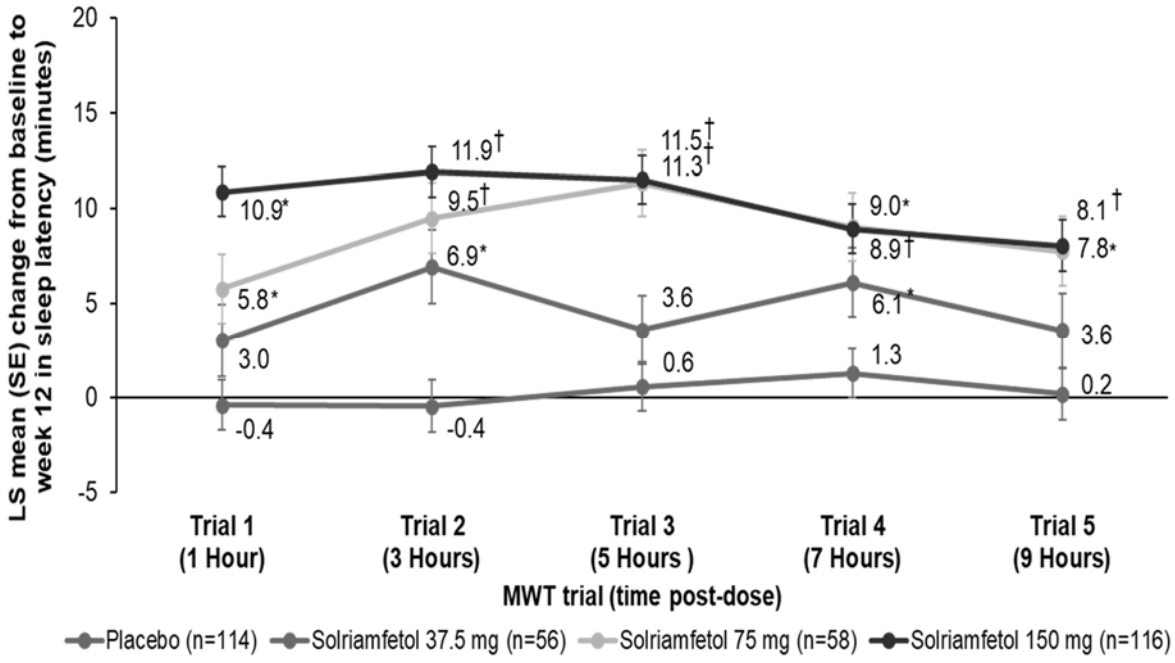
B.2.6.1.6.2 MWT effect sizes (Post-hoc analysis)

- At week 12, effect sizes (Cohen's d) were 0.4, 0.9, 1.2 for solriamfetol 37.5, 75, and 150 mg, respectively.

B.2.6.1.6.3 Time course of efficacy on MWT: maintenance of wakefulness throughout the day

- At week 12, the change from baseline in sleep latency in each of the five individual 40-minute MWT trials was significantly greater with solriamfetol 75 mg ($p<0.05$) and 150 mg ($p<0.0001$) doses compared with placebo (pairwise comparisons versus placebo), demonstrating the ability of solriamfetol to improve wakefulness from 1 to 9 hours after dosing.
- Based on the prespecified testing sequence, the 37.5 mg dose of solriamfetol only showed a statistically significant difference compared with placebo for trial 2 ($p<0.05$); the improvement observed for trial 4 was therefore only of nominal significance (nominal $p<0.05$) (Figure 7).

Figure 7: TONES 3: 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 minutes duration, were performed at 2-hour intervals beginning 2 hours after awakening and 1 hour after dosing at the approximate times post-dose shown in parentheses. The result at trial 4 for 37.5 mg was of nominal significance based on the prespecified testing sequence.
*p<0.05, **p<0.0001 vs. placebo.
Source: Schweitzer 2019 (98).

B.2.6.1.6.4 Patients achieving normal MWT sleep latency (post-hoc analysis)

- 19.4 minutes has been reported as the lower limit of normal in healthy patients (114); based on this value a 20-minute cut-off was set to demonstrate the clinical relevance of improvements observed with solriamfetol on the MWT.
- At week 12, the percentage of patients in each solriamfetol group with a mean MWT sleep latency of ≥20 minutes was 34.0, 53.6, and 62.5% of patients in the 37.5, 75, and 150 mg dose groups, respectively, compared with only 23.4% in the placebo arm.
- In contrast, at baseline, the percentage of patients with MWT sleep latency ≥20 minutes was 14.8, 15.8 and 13.9% for those randomised to solriamfetol 37.5, 75 and 150 mg dose, respectively compared with 18.0% of those randomised to placebo.

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

- Dose-dependent improvement on the PGI-c and CGI-c was observed for patients in the solriamfetol groups compared with placebo as early as week 1, representing patient-assessed (PGI-c) and clinician-assessed (CGI-c) improvements in the patient's condition.
- For the PGI-c, significantly higher percentages were observed for solriamfetol 75 mg (65.5–79.3%; all $p<0.05$), and 150 mg (78.3–89.7%; all $p<0.0001$) doses across all time points from baseline to week 12 versus placebo (47.4–57.0%). Of patients in the solriamfetol 37.5 mg arm, numerical improvements were observed with 55.4–60.7% improved across time points.
- For the CGI-c, significantly higher percentages were observed for solriamfetol 150 mg (75.7–90.5%; all $p<0.0001$) at all time points from baseline to week 12, versus placebo (46.5–52.6%). For solriamfetol 75 mg, percentages were significantly higher (70.7–77.6%; $p<0.05$) at all time points, except week 1 (60.3%). Of patients in the solriamfetol 37.5 mg arm, 55.4–62.5% were improved; this effect was significant at week 1 (62.5% vs 46.5% for placebo).

B.2.6.1.8 Exploratory endpoint: Changes in use of primary OSA therapy

- All parameters for the use of primary OSA therapy remained relatively constant throughout the study.

- Mean (SD) change in the percentage of nights participants used a primary OSA therapy from baseline to weeks 9–12 was 0.8% (12.1) for placebo (n=69) and 1.1% (12.0) for the combined solriamfetol group (n=218).
- Similarly, for participants who had electronically retrievable data, the mean (SD) change in the average number of hours per night patients used their OSA device from baseline to weeks 9–12 was -0.3 (0.9) and -0.3 (1.2) for placebo (n=43) and the combined solriamfetol group (n=133), respectively.
- There were no meaningful changes in the percentage of nights, or number of hours per night, that patients used their primary OSA therapy for any dose of solriamfetol compared with placebo.

B.2.6.1.9 Exploratory endpoint: Polysomnography parameters

- There were no statistically significant or clinically meaningful changes in polysomnography (PSG) parameters of total sleep time, number of awakenings, or wake after sleep onset at week 12 in the mITT Population.

B.2.6.1.10 Secondary endpoints: health-related quality of life

FOSQ-10

- Solriamfetol dose dependently improved functional status based on change from baseline to week 12 on the sleep specific FOSQ-10 questionnaire.
- Improvements versus placebo were statistically significant for the 150 mg dose (Table 14).

SF-36v2

- Statistically significant improvements from baseline at week 12 in Physical Component Summary (PCS) scores were observed for solriamfetol 150 mg. Changes from baseline to week 12 in the Mental Component Summary (MCS) scores for solriamfetol 37.5 mg, 75 mg and 150 mg were similar, although only the 150 mg dose reached statistical significance versus placebo (Table 14). Changes did not exceed the minimal clinically important difference (MCID).
- Among the individual SF-36 domains, the largest effects of solriamfetol were observed on Vitality and Role Physical, with the solriamfetol 150 mg dose

significantly improving Vitality, Role Physical, General Health, Social Functioning and Mental Health Scores versus placebo at week 12 ($p<0.05$).

EQ-5D-5L

- Effects of solriamfetol on the EQ-5D VAS appeared to be dose dependent but were not significantly different from placebo. There were no significant effects on the EQ-5D-5L index value, however within the placebo and solriamfetol arms, [redacted] and [redacted] of patients, respectively, had a utility score of 1 at baseline, and mean (SD) utility scores were high at baseline: [redacted], and [redacted], respectively, suggesting limited capacity for improvement with treatment.

Table 14: TONES 3: HRQoL endpoints (mITT Population)

	Placebo N=114	Solriamfetol		
		37.5 mg N=56	75 mg N=58	150 mg N=116
Change in FOSQ-10 total score from baseline to week 12				
LS mean (SE)	1.72 (0.241)	1.99 (0.345)	2.47 (0.331)	2.95 (0.236)
LS mean difference vs placebo		[redacted]	[redacted]	1.22
95% CI		[redacted]	[redacted]	0.57, 1.88
p value		[redacted]	[redacted]	[redacted]
Change in SF-36v2 physical component summary score from baseline to week 12				
LS mean (SE)	1.43 (0.608)	1.64 (0.876)	1.99 (0.838)	3.50 (0.598)
LS mean difference vs. placebo		[redacted]	[redacted]	2.07
95% CI		[redacted]	[redacted]	0.42 to 3.72
p value (nominal)		[redacted]	[redacted]	[redacted]
Change in SF-36v2 mental component summary score from baseline to week 12				
LS mean (SE)	1.05 (0.703)	2.65 (1.012)	2.94 (0.965)	3.10 (0.691)
LS mean difference vs. placebo		[redacted]	[redacted]	2.05
95% CI		[redacted]	[redacted]	0.14 to 3.96
p value (nominal)		[redacted]	[redacted]	[redacted]

Abbreviations: CI, confidence interval; CSR, clinical study report; FOSQ-10, 10-item Functional Outcomes of Sleep Questionnaire; HRQoL, health related quality of life; LS, least squares; mITT, modified intent to treat; SD, standard deviation; SE, standard error; SF-36v2, 36-item Short-Form Health Survey version 2; TONES, Treatment of Obstructive sleep apnoea and Narcolepsy Excessive Sleepiness.
Source: Bogan 2017 (123); Benes 2017 (124); CSR Table 26 and Table 14.2.7.2 (97); Weaver 2020 (100).

B.2.6.1.11 Work productivity and activity impairment

At baseline in TONES 3, 48.8% of patients were employed and reported substantial impact of OSA on their work and activity. Dose-dependent changes were observed for the Work Productivity and Activities Impairment: Specific Health Problem (WPAI:SHP) questionnaire, with solriamfetol 150 mg resulting in significantly decreased presenteeism, overall work impairment and activity impairment (outside of work) at week 12 compared with placebo. Numerical improvements in absenteeism, presenteeism, overall work impairment and activity impairment outside of work were observed for all other solriamfetol doses.

B.2.6.1.12 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 all solriamfetol doses. Significant improvements on both co-primary endpoints were observed for all solriamfetol doses and at all timepoints, except solriamfetol 37.5 mg at week 1 for MWT and week 8 for ESS. Improvements observed at week 1 (the first point of measurement in the study) were maintained across the duration of the study, indicating that patients did not build a tolerance to solriamfetol treatment over 12 weeks. The effects of solriamfetol 75 mg and 150 mg were sustained throughout the day: at week 12, significant improvements in wakefulness versus placebo were apparent in each of the individual five MWT trials throughout the day (nominal $p<0.05$). For the solriamfetol 37.5 mg dose, significant improvements were observed on Trial 2 and 4, and numerical but not significant improvements were observed at Trials 1, 3 and 5.

B.2.6.2 TONES 5 (Long-term Phase 3 study)

This submission pertains to solriamfetol for treating patients with EDS due to OSA, and only results for the OSA population are presented. Results for the overall population are presented in Appendix L.

Data for patients with narcolepsy are not presented but were presented in the appraisal of solriamfetol for treating EDS due to narcolepsy (ID1602). Results are generally presented as the pre-specified combined dose arm (75, 150 and [unlicensed] 300 mg), with the exception of ESS change over time, for which a separate analysis stratified by dose has also been presented.

As described previously (Section B.2.3.2.2), patients in TONES 5 had either OSA or narcolepsy (Safety Population: n=417 OSA; n=226 narcolepsy), 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.

B.2.6.2.1 Treatment exposure in TONES 5

Across the entire duration of the study, patients with OSA 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. 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.2.6.2.2 Open-label phase

B.2.6.2.2.1 Secondary efficacy endpoint: ESS

- During the open-label phase, the long-term maintenance of solriamfetol efficacy was demonstrated in the OSA population through sustained reduction in mean ESS scores, indicating reduced EDS.
- These improvements in EDS were maintained for up to 40 weeks in Group A (Figure 8), and up to 52 weeks in Group B (Figure 9).
- Patients with OSA who were treated with solriamfetol (combined group) achieved clinically meaningful reductions in mean ESS (defined as ≥3 point decrease) after 2 weeks of treatment (week 2 was the first point of measurement in the study), that were maintained through 40 weeks for Group A and 52 weeks for Group B:
  - Group A[j] mean change from baseline to week 2: [redacted], and week 40: [redacted]
  - Group B[j] mean change from baseline to week 2: [redacted], and week 52: [redacted]

Results by dose and patient group

Results for the change in ESS from baseline to week 2 (the first point of measurement in the study), and to week 40 and 52 for the solriamfetol 75 and 150 mg doses, respectively, are provided in Table 15, showing that the beneficial treatment effect of solriamfetol was maintained long term with both doses.

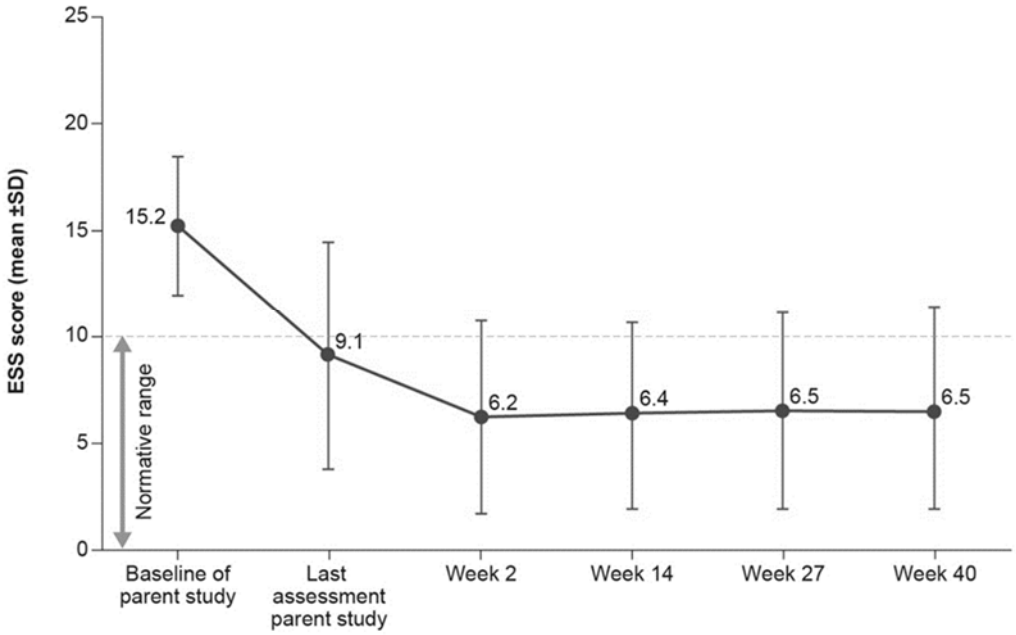
[j] Group A included patients from TONES 2 and TONES 3; the baseline values used for analysis were the baseline values of the parent study. Group B included patients from TONES 4, or one of the phase 2 studies: 15 004, 15-005, or ADX-N05-201, or TONES 1; the baseline values used for analysis were the baseline values of TONES 5.

Table 15. TONES 5: Change in mean ESS scores from baseline for patients with OSA 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]

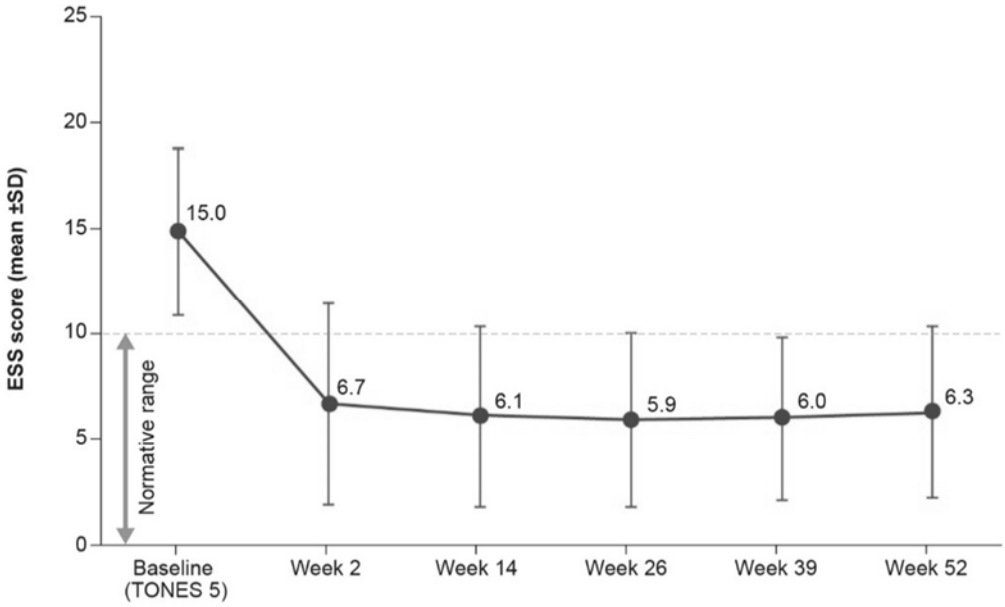
Abbreviations: ESS, Epworth Sleepiness Scale; NA, not applicable; OSA, obstructive sleep apnoea; SD, standard deviation; TONES, Treatment of Obstructive sleep apnoea and Narcolepsy Excessive Sleepiness.
Data presented as mean (SD).
† Baseline defined as the baseline of the parent study for Group A and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

Figure 8. TONES 5: Mean (SD) ESS score for patients with OSA in Group A (n=333) 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.
*p=0.0005 vs. placebo; **p=0.0001 vs. placebo.
Source: Malhotra 2019 (102)

Figure 9. TONES 5: Mean (SD) ESS score for patients with OSA in Group B (n=84) 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.
*p=0.0005 vs. placebo; **p=0.0001 vs. placebo.
Source: Malhotra 2019 (102)

B.2.6.2.2.2 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 OSA had improvements in the PGI-c and CGI-c at week 2 (≥94.6% and ≥96.1%, respectively), maintained at similar percentages at each assessment; at the final assessment, 90.4–96.4% of patients reported an improvement in PGI-c, and 91.6–97.6% were reported as improved on the CGI-c (combined range across Groups A and B).

B.2.6.2.2.3 Secondary endpoints: HRQoL

FOSQ-*10*

- During the open-label phase, mean FOSQ-10 scores increased from baseline in the OSA population for patients in Group A, and Group B.
- The increased FOSQ-10 scores were observed by week 14 of treatment, and were maintained for the duration of solriamfetol treatment, in Group A and B, indicating patients had less difficulty in performing every day activities (Figure [redacted] and Figure 11, respectively).

Figure 10. TONES 5: Mean (SD) FOSQ-10 scores for patients with OSA in Group A (n=333) during the open-label phase (Safety)

Abbreviations: CSR, clinical study report; FOSQ-10, 10-item Functional Outcomes of Sleep Questionnaire; OSA, obstructive sleep apnoea; SD, standard deviation; TONES, Treatment of Obstructive sleep apnoea and Narcolepsy Excessive Sleepiness.
Source: Weaver 2019 (103), CSR Table 11.4.1.2.4 (101).

Figure 11. TONES 5: Mean (SD) FOSQ-10 scores for patients with OSA in Group B (n=84) during the open-label phase (Safety)

Abbreviations: CSR, clinical study report; FOSQ-10, 10-item Functional Outcomes of Sleep Questionnaire; OSA, obstructive sleep apnoea; SD, standard deviation; TONES, Treatment of Obstructive sleep apnoea and Narcolepsy Excessive Sleepiness.
Source: Weaver 2019 (103); CSR Table 11.4.1.2.4 (101).

SF-36v2

- Solriamfetol (combined arm including the unlicensed 300 mg dose) improved both PCS and MCS scores of the SF-36 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-36 had limited sensitivity to detect change in this population. This may be due to similar reasons as those noted for the EQ-5D response (Section B.3.2).
  - Patients with OSA in Group A achieved numerical improvements from baseline to week 40 in the PCS (+3.7) and MSC (+4.5), in addition to a 9.6 point improvement in the vitality domain. Similar results were observed for patients in Group B.

EQ-5D-5L

- Compared with baseline, [redacted] for each of the 5 dimensions of the EQ-5D-5L (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression) when measured at various timepoints up to the final evaluation (Group A, week 40; Group B, week 52).
- [redacted] beginning at the first post-treatment timepoint, and were maintained through to the final evaluation for both Group A and Group B (mean changes ranged from [redacted], respectively).

B.2.6.2.2.4 Work productivity and activity impairment

- 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:
- For patients with OSA in Group A and Group B (103):
  - Presenteeism, overall work impairment and impairment of activities outside of work were reduced by at least 25% from baseline of the parent study.

- These improvements were observed by week 14 of treatment and sustained throughout the study (up to 52 weeks).
- The rates of absenteeism (work time missed) were low at baseline in both Group A and B at baseline ([redacted] and [redacted], respectively) and small decreases from baseline were observed throughout the study with solriamfetol treatment ([redacted]% and [redacted]%, respectively).

B.2.6.2.3 Randomised withdrawal phase

B.2.6.2.3.1 Primary efficacy endpoint: ESS

- All primary and secondary endpoints for the subgroup of patients with OSA were met in the 2-week randomised withdrawal phase.
- During this phase, patients with OSA 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] to [redacted]; p<0.0001) (Table 16).
- 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 12).
- The primary and secondary endpoints were met in the overall population; full results are reported in Appendix L.

Figure 12. TONES 5: ESS scores for participants with OSA (Group A and Group B) who entered the randomised withdrawal phase (mITT Population)

Abbreviations: CI, confidence interval; CSR, clinical study report; ESS, Epworth Sleepiness scale; LS, least squares; mITT, modified intent to treat; OSA, obstructive sleep apnoea; SD, standard deviation; TONES, Treatment of Obstructive sleep apnoea and Narcolepsy Excessive Sleepiness.
† Values are for the baseline of parent study for Group A and at baseline of current study for Group B); the randomised withdrawal phase included participants from both groups.
Source: CSR Table 20 and Table 14.2.1.2a (101).

Table 16. TONES 5: primary analysis – change in ESS from efficacy baseline to end of randomised withdrawal phase for patients with OSA† (mITT Population)

	Placebo N=101	Solriamfetol combined N=101
LS mean (SE)		
LS mean difference		
95% CI		
p value‡		

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 based on ANCOVA
Analysis conducted in mITT .
Source: CSR Table 20 (101).

Secondary analysis of the primary endpoint

- [redacted]

B.2.6.2.3.2 Secondary endpoints: PGI-c and CGI-c

- During the 2-week withdrawal phase, patients with OSA who were randomised to placebo had a loss of efficacy whereas those randomised to solriamfetol (including the unlicensed 300 mg dose) maintained treatment efficacy.
  - [redacted]% of patients in the placebo group worsened 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 randomised to placebo had experienced worsening compared with patients randomised to solriamfetol ([redacted]% vs [redacted]%, respectively; [redacted]).

B.2.6.2.3.3 Health-related quality of life (FOSQ-10)

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

B.2.6.2.4 TONES 5 conclusion

Long-term efficacy for EDS, as measured by ESS, was maintained in patients with OSA 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 OSA 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] on ESS; [redacted]). TONES 5 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.2.6.3 TONES 4 (Supporting Phase 3 randomised withdrawal study)

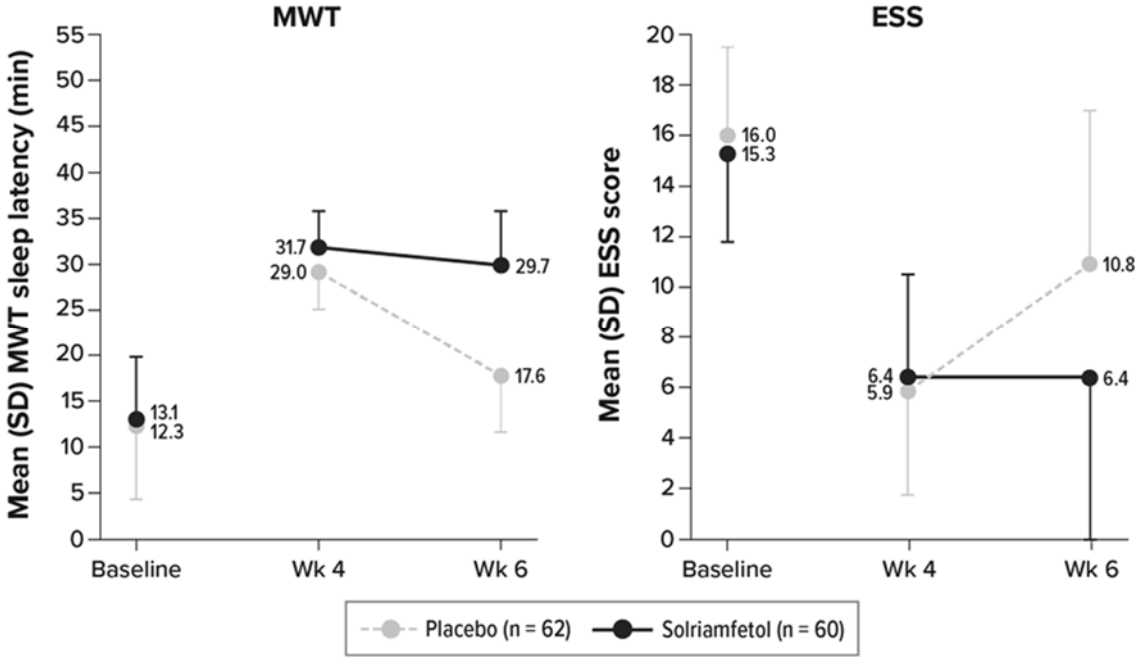
- Patient-reported ESS scores decreased (indicating reduced sleepiness) after 4 weeks of solriamfetol, from 15–16, to approximately 6, which is within the normal range for ESS (Table 6).
- MWT scores increased (indicating increased wakefulness) after 4 weeks of solriamfetol, from approximately 12–13 minutes, to approximately 30 minutes.

B.2.6.3.1 Co-primary efficacy endpoints: change in ESS and MWT from week 4 to week 6

The co-primary endpoints of change from week 4 to week 6, in ESS and MWT scores were met. Over this 2 week withdrawal phase:

- Patients who continued receiving solriamfetol maintained efficacy and showed minimal changes in ESS and MWT whereas those patients who were switched to placebo experienced worsening of their ESS and MWT scores (Figure 13).
- There were statistically significant differences between solriamfetol and placebo for both the MWT and ESS at week 6, in favour of solriamfetol (Table 17).
  - The LS (SE) mean change from weeks 4 to 6 for the ESS score was 4.5 (0.7) for placebo compared with -0.1 (0.67) for solriamfetol, and the LS mean difference was -4.6 (95% CI, -6.4 to -2.8; p<0.0001).
  - The LS (standard error [SE]) mean change from weeks 4 to 6 for the MWT mean sleep latency was −12.1 (1.3) minutes for placebo compared with −1.0 (1.4) minute with solriamfetol, and the LS mean difference was 11.2 minutes (95% CI, 7.8 to 14.6; p<0.0001).

Figure 13. TONES 4: Values for the co-primary endpoints MWT and ESS for patients who entered the randomised withdrawal phase (mITT Population)



Abbreviations: ESS, Epworth Sleepiness Scale; min, minutes; mITT, modified intent to treat; MWT, Maintenance of Wakefulness Test; SD, standard deviation; Wk, week.
Source: Strollo 2019 (105)

Table 17. TONES 4: Co-primary and key secondary efficacy endpoints (week 6; mITT Population)

Characteristic†	Double Blind Withdrawal Phase	
	Placebo N=62	Combined solriamfetol N=60
Primary endpoints		
Change in MWT from efficacy baseline (week 4) to week 6		
LS mean (SE)	-12.1 (1.3)	-1.0 (1.4)
LS mean difference vs. placebo		11.2
95% CI		7.8 to 14.6
p value‡		<0.0001
Change in ESS from efficacy baseline (week 4) to week 6		
LS mean (SE)	4.5 (0.7)	-0.1 (0.7)
LS mean difference vs. placebo		-4.6
95% CI		-6.4 to -2.8
p value‡		<0.0001
Key Secondary Endpoint		
Patients reported as worse† on PGI-c from efficacy baseline (week 4) to week 6.		
Yes, n (%)	31 (50.0)	12 (20.0)

Characteristic†	Double Blind Withdrawal Phase	
	Placebo N=62	Combined solriamfetol N=60
Difference [Yes] from placebo, % (95% CI)		-30.0 (-46.0 to -14.0)
p value§		0.0005

Abbreviations: CI, confidence interval; ESS, Epworth Sleepiness Scale; LOCF, last observation carried forward; LS, Least Squares; mITT, modified intent to treat; MWT, Maintenance of Wakefulness Test; OSA, obstructive sleep apnoea; PGI-c, Patient Global Impression of Change; SE, standard error; TONES, Treatment of Obstructive sleep apnoea and Narcolepsy Excessive Sleepiness.
†Minimally, much, or very much worse as measured from efficacy baseline to week 6.
‡ p value for MWT and ESS based on analysis of covariance with change from week 4 to week 6 as the response variable and fixed effect model terms of treatment, efficacy baseline (week 4 value) and randomisation stratification factor (compliant and non-compliant to primary OSA therapy); missing data imputed using LOCF.
§ p value for PGI-c based on a chi-square test; missing data imputed using LOCF.
Source: Strollo 2019 (105).

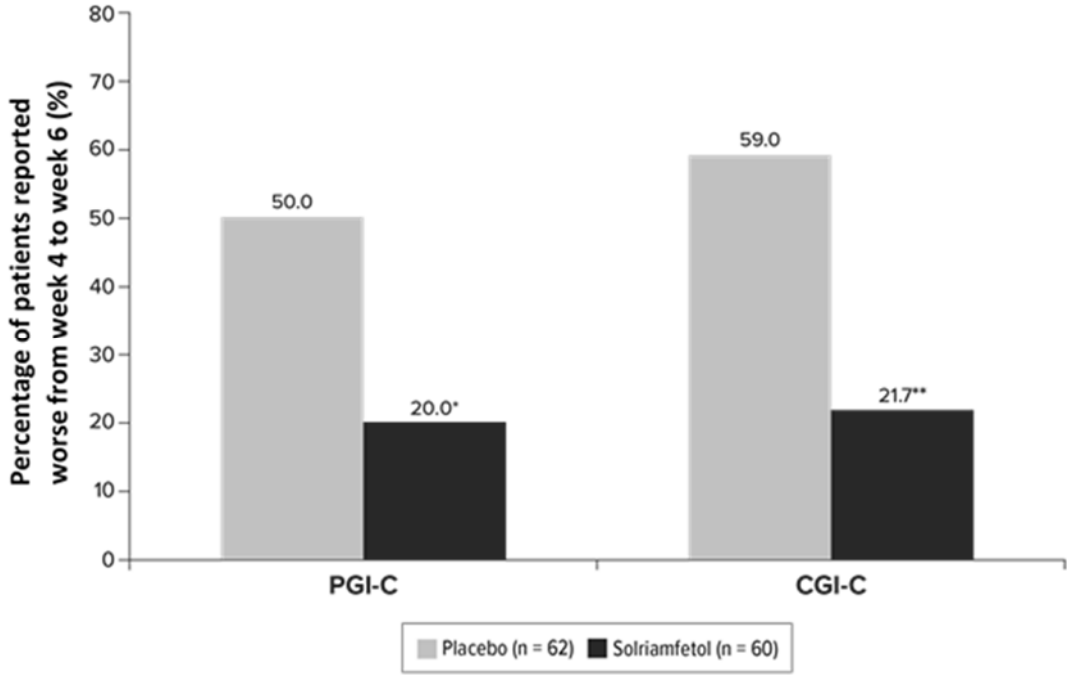
B.2.6.3.2 Secondary analysis of the co-primary endpoints

- [redacted].

B.2.6.3.3 Key secondary endpoint: PGI-c at week 6

- As compared with study baseline [redacted] receiving solriamfetol (Safety Population) were at least minimally improved ([redacted]%, minimally, much or very much improved, respectively), [redacted] patient was minimally worse and no patients were much/very much worse on the PCI-C scale.
- At the end of the randomised withdrawal phase (week 6), 50.0% of patients on placebo experienced worsening on the PGI-c compared with only 20.0% of patients who continued solriamfetol (Difference, -30.0; 95% CI, -46.0 to -14.0; p<0.001) (Figure 14).

Figure 14. TONES 4: percentage of patients who had overall worsening of their condition in the double-blind randomised-withdrawal phase (mITT Population)



Abbreviations: CGI-c, Clinical Global Impression of Change; LOCF, last observation carried forward; mITT, modified intent to treat; PGI-c, Patient Global Impression of Change; TONES, Treatment of Obstructive sleep apnoea and Narcolepsy Excessive Sleepiness.
*p=0.0005 vs. placebo; **p=0.0001 vs. placebo.
§ p values based on a chi-square test; missing data are imputed using LOCF.
Adapted from Strollo 2019 (105)

B.2.6.3.4 Secondary endpoints: CGI-c

- At week 4, [redacted] on the CGI-c scale. The majority of patients ([redacted] were reported to be minimally, much, or very much improved ([redacted], minimally, much or very much improved, respectively) and [redacted] patients were much/very much worse.
- At the end of the randomised withdrawal phase, 59.0% of participants who switched to placebo worsened (as rated by physicians), compared with only 21.7% who continued using solriamfetol (Difference, -37.3%; 95% CI, 53.5 to 21.2; p<0.0001) (Figure 14).

B.2.6.3.5 Secondary endpoints: FOSQ-10

- FOSQ-10 scores improved from a mean baseline of 13.5–13.7, to mean scores of 17.6–17.8, after 4 weeks of treatment.

- At the end of the randomised withdrawal phase (week 6), mean (SD) FOSQ-10 scores were 16.4 (2.9) for placebo, and 17.4 (3.0) for solriamfetol, significantly favouring solriamfetol (p<0.05) (Table 18).

Table 18. Summary of analysis of change in total FOSQ-10 score during the Double Blind Withdrawal Phase (mITT Population)

Characteristic†	Placebo N=62	Solriamfetol N=60
Change from efficacy baseline (week 4) to week 6		
LS mean (SE)	-1.3 (0.4)	-0.15 (0.4)
LS mean difference		1.2
95% CI		0.2 to 2.1
p value†		<0.05

Abbreviations: CI, confidence interval; FOSQ-10, 10-item Functional Outcomes of Sleep Questionnaire; LS, least squares; mITT, modified intent to treat; OSA, obstructive sleep apnoea; SE, standard error.
† p value based on [redacted].
Source: Strollo 2019 (105).

B.2.6.3.6 Exploratory endpoints: FOSQ-10 subscale scores

- For the solriamfetol group, [redacted] FOSQ-10 subscale scores (activity level, general productivity, social outcome, intimacy and sexual relationships, and vigilance,) had changes that indicated [redacted] during the stable-dose phase (from baseline to the end of week 4).
- At efficacy baseline (end of week 4), FOSQ-10 subscale scores for the placebo and solriamfetol groups [redacted]. By the end of the randomised withdrawal phase, values for the FOSQ-10 subscales had [redacted].
- However the changes in scores were [redacted] for the placebo group, suggesting that patients who were switched to placebo experienced a [redacted] functional improvement compared with those patients who continued their stable dose of solriamfetol treatment.

B.2.6.3.7 Exploratory endpoints: changes in primary OSA therapy

- During the open-label phases of the study, [redacted] used a primary OSA therapy and maintained stable use of that therapy.

- Patients in the withdrawal phase [redacted] to their primary OSA therapy. At efficacy baseline (week 4), the mean percentage of nights using therapy was [redacted] in the placebo group, and [redacted] in the solriamfetol group, with minimal change at week 6 (mean increase [redacted] respectively).
- There was [redacted] between groups in the change in percentage of nights that patients used a primary OSA therapy [redacted]

B.2.6.3.8 TONES 4 conclusion

The results from TONES 4 demonstrated the efficacy of solriamfetol in reducing sleepiness and improving wakefulness (as measured using ESS and MWT, respectively) during a 2 week Titration Phase and 2 Week Stable Dose phase. This study further demonstrated that the efficacy of solriamfetol in treating EDS was retained with continued treatment but that treatment withdrawal was associated with rapid (within 2 weeks) loss of efficacy and trend towards baseline status. The results from the randomised, placebo-controlled withdrawal phase of TONES 4 supports those observed for TONES 5 and indicates that patients do not experience treatment waning over time, and that discontinuation of solriamfetol treatment is not associated with rebound hypersomnia or withdrawal effects.

B.2.7 Subgroup analysis

B.2.7.1 TONES 3 (Pivotal placebo-controlled trial)

Pre-specified subgroup analyses were based on the mITT Population and were performed using the same mixed effects repeated measures (MMRM) method used for the primary endpoint analyses (Section B.2.4.2). Pre-defined subgroups were compliant use of primary OSA therapy at screening, [redacted]. A summary of results is provided below, with full results provided in Appendix E.

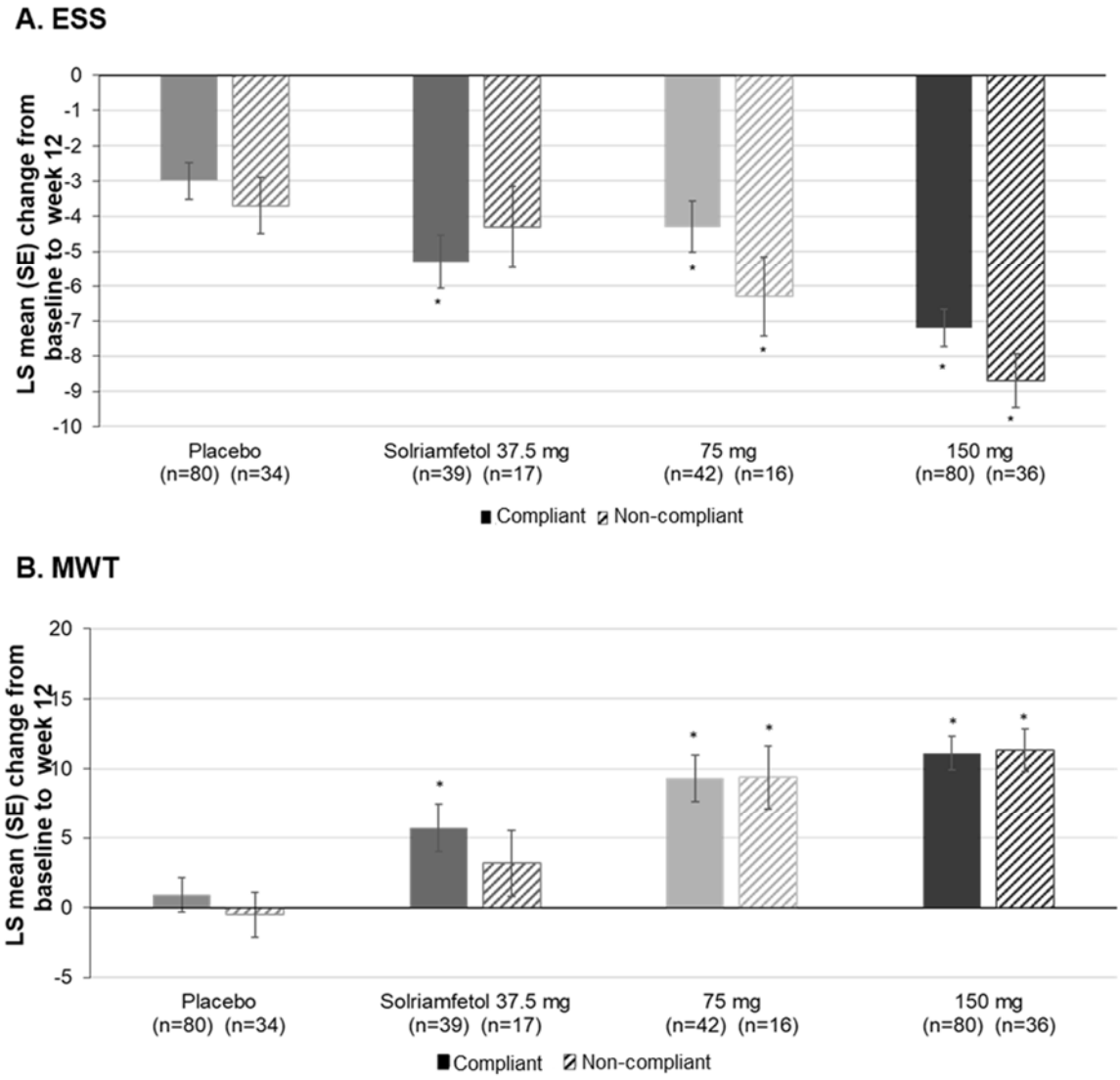
- **Compliance to OSA therapy:** For the subgroups of patients who were compliant or non-compliant to primary OSA therapy, there were no meaningful differences in response to solriamfetol versus placebo for the co-primary endpoints of MWT and ESS (LS means for change in MWT sleep latency or ESS score from baseline to week 12; see Figure 15).
- [redacted] Analyses by [redacted] specifically for [redacted] placebo, [redacted]; solriamfetol, [redacted] reflected the overall mITT Population. For [redacted] the analysis of [redacted] were not conducted due to the very small patient numbers (Table 19).

Table 19. Patient numbers [redacted] for TONES 3

[redacted]	Placebo	Solriamfetol 37.5 mg	Solriamfetol 75 mg	Solriamfetol 150 mg	Solriamfetol 300 mg (unlicensed)
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: TONES, Treatment of Obstructive sleep apnoea and Narcolepsy Excessive Sleepiness; [redacted]

Figure 15. Subgroup analysis: MWT sleep latency and ESS change from baseline to week 12 in patients compliant or non-compliant to primary OSA therapy (mITT Population)



Abbreviations: ESS, Epworth Sleepiness Scale; LS, least squares, mITT, modified intent to treat; MWT, Maintenance of Wakefulness Test; OSA, obstructive sleep apnoea; SE, standard error.
* p<0.05 (nominal).
Source: Schweitzer 2018 (125).

B.2.7.2 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] (Section B.2.4.2). Pre-specified subgroups were compliant or non-compliant use of primary OSA therapy at randomisation in a previous study (TONES 3/4) or at baseline in the current study (TONES 5), and [redacted]). OSA and Narcolepsy were

also specified and relevant data have already been presented in the main results for TONES 5 in Section B.2.6.2.

A summary of results is provided below, with full results in Appendix E.

- For the 2-week randomised withdrawal phase, [redacted] was observed in ESS scores:
- [redacted]
- When the same analyses were performed using the Per Protocol Population, results were consistent with those observed in the mITT Population.

B.2.7.3 TONES 4 (Supportive comparative Phase 3 study)

Pre-specified subgroup analyses to evaluate MWT and ESS were performed on the mITT Population, using the same ANCOVA method as that used for the primary analyses (Section B.2.4.2). Pre-specified subgroups were compliant use of primary OSA therapy at randomisation, and [redacted]).

A summary of results is provided below, with full results in Appendix E

- Comparisons between the placebo and combined solriamfetol treatment groups during the randomised withdrawal phase (week 4 to week 6) showed a statistical significance favouring solriamfetol ($p<0.05$).
- Significant differences were observed between patients who were compliant or non-compliant to a primary OSA therapy, with larger mean differences observed in the non-compliant group for both MWT and ESS scores.

B.2.8 Meta-analysis

As the efficacy evidence used in the economic model is based on the TONES 3 trial (and a clinical SLR was not conducted) therefore a meta-analysis is not applicable for the current submission.

B.2.9 Indirect and mixed treatment comparisons

This submission compares solriamfetol as an add-on treatment to standard of care compared with standard of care without solriamfetol, using trial data from TONES 3. As such as an indirect treatment comparison is not applicable and was not carried out for the current submission.

B.2.10 Adverse reactions

Across the entire clinical development programme for solriamfetol, [redacted] unique patients have been exposed to solriamfetol (including the unlicensed 300 mg dose), as of [redacted], including patients with OSA, narcolepsy, or major depressive disorder, and healthy subjects.

In the clinical trial programme for solriamfetol, 614[k] unique patients with OSA were treated with solriamfetol (all doses, including the unlicensed 300 mg dose): 359 were exposed to solriamfetol for at least 6 months, and 186 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 unlicensed 300 mg dose) during the open label phase was [redacted] or approximately [redacted], and in the OSA population was [redacted].

An overview of AE data from the three Phase 3 trials that enrolled patients with EDS and OSA is provided by treatment arm for the Safety Populations in TONES 3 (Table 20), TONES 5 (Table 21), and TONES 4 (Table 22).

[k] For TONES 5, patients were eligible for inclusion if they had completed previous studies, including TONES 3 and TONES 4, hence some patients appear in the safety populations of TONES 3 or TONES 4 as well as TONES 5; as such the sum of the individual safety populations from the three trials (N=946) is larger than the number of unique patients who received solriamfetol (N=614).

A safety overview, including narratives of common AEs, serious AEs, discontinuations due to AEs, and AEs of special interest is provided. Where possible this narrative is based on the three Phase 3 OSA trials. Broader observations from pooled safety data, as submitted for EMA marketing authorisation and including evidence from the wider evidence base (for example, patients with narcolepsy or from the broader clinical trial program) are also included, where appropriate.

All AEs in the clinical programme for solriamfetol were [redacted] (for TONES 5 this meant AEs that began or worsened during TONES 5, not the parent study).

B.2.10.1 Safety overview

In general, AEs are dose related, with the unlicensed 300 mg dose having the greatest rates of AEs, and appear to be reversible. Although the 300 mg dose is unlicensed, the safety data in this submission includes reference to the 300 mg dose to provide a complete description of solriamfetol safety.

- Analysis of AEs showed that solriamfetol in the proposed therapeutic dose range (37.5 to 150 mg) was well tolerated by most patients.
- Among the 755 patients with OSA (614 unique patient exposures) treated with solriamfetol (including the unlicensed 300 mg dose) during TONES 3–5, there was one death (at the 300 mg dose and unrelated to solriamfetol) and serious AEs were reported in 24 patients, for all doses including the unlicensed 300 mg dose: TONES 3, n=3 (0.8%); TONES 5, n=21 (5.0%); TONES 4, n=0 (0.0%). Excluding the unlicensed 300 mg dose, serious AEs occurred in [redacted] patients: TONES 3, n=3; TONES 5, n=[redacted], TONES 4, n=0.

- The majority of AEs in patients with OSA were classified as mild[l] or moderate[m]:
  - TONES 3: 94.6% (solriamfetol 37.5 mg, [redacted]%, solriamfetol 75 mg, [redacted]%, and solriamfetol 150 mg, [redacted]%)
  - TONES 4: [redacted]% (all study phases; including the unlicensed 300 mg dose)
  - TONES 5: [redacted]% (including the unlicensed 300 mg dose)
- The incidence of AEs leading to discontinuation of solriamfetol and/or study withdrawal (including the unlicensed 300 mg dose) was <10% (TONES 3: 7.0%; TONES 5: 8.6%; TONES 4: 3.4%) in the OSA population and was dose-related; this was consistent across each population included in the clinical trial programme (narcolepsy/OSA combined, major depressive disorder (MDD), and healthy volunteers).
- There was no evidence to suggest the late emergence of AEs with long-term administration of solriamfetol.
- The AE profile of solriamfetol is consistent with the expected pharmacology of a DNRI, and the well characterised pharmacokinetic characteristics of solriamfetol, and 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 majority of these AEs were mild or moderate in nature, occurred within the first two weeks of initiating treatment, and resolved for the majority of patients with a median duration of less than two weeks. The nature of the AEs is such that they can be detected, monitored, and managed with routine measures and treatments in clinical practice, or if needed, addressed through dose reduction or discontinuation, as described in the SmPC (Appendix C).

[l] Symptom(s) barely noticeable to subject or does not make subject uncomfortable; does not influence performance or functioning; prescription drug not ordinarily needed for relief of symptom(s) but may be given.

[m] Symptom(s) of a sufficient severity to make subject uncomfortable; performance of daily activities is influenced; treatment for symptom(s) may be needed.

Table 20: TONES 3: Summary of AEs (Safety Population)

Adverse event, n (%)	Placebo N=119	Solriamfetol 37.5 mg N=58	Solriamfetol 75 mg N=62	Solriamfetol 150 mg N=117
Any AE	57 (47.9)	37 (63.8)	30 (48.4)	83 (70.9)
Any treatment-related AE†	[redacted]	[redacted]	[redacted]	[redacted]
Serious AE	2 (1.7)	2 (3.4)	0	1 (0.9)
Any treatment-related serious AEs†	[redacted]	[redacted]	[redacted]	[redacted]
Deaths	0	0	0	0
AE leading to study drug and study discontinuation	4 (3.4)	3 (5.2)	2 (3.2)	5 (4.3)
AEs occurring in ≥5% of patients (any treatment group)				
Headache	10 (8.4)	4 (6.9)	5 (8.1)	10 (8.5)
Nausea	7 (5.9)	3 (5.2)	3 (4.8)	10 (8.5)
Decreased appetite	1 (0.8)	1 (1.7)	3 (4.8)	9 (7.7)
Anxiety	0	1 (1.7)	2 (3.2)	6 (5.1)
Nasopharyngitis	8 (6.7)	2 (3.4)	1 (1.6)	7 (6.0)
Diarrhoea	1 (0.8)	1 (1.7)	3 (4.8)	5 (4.3)
Dry mouth	2 (1.7)	1 (1.7)	1 (1.6)	5 (4.3)
Insomnia	2 (1.7)	1 (1.7)	0	3 (2.6)
Feeling jittery	0	3 (5.2)	3 (4.8)	1 (0.9)
Sinusitis	3 (2.5)	1 (1.7)	4 (6.5)	0
Irritability	0	3 (5.2)	0	4 (3.4)
Pruritus	0	3 (5.2)	0	1 (0.9)

Abbreviations: AE, adverse event; CSR, clinical study report; TONES, Treatment of Obstructive sleep apnoea and Narcolepsy Excessive Sleepiness.
All AEs are [redacted]
† Related or suspected related to study drug.
Source: Schweitzer 2019 (98); CSR Table 31 and Table 33 (97).

Table 21: TONES 5: Summary of adverse events (Safety Population)

Adverse event	Patients receiving solriamfetol (all doses), n (%)	
	Overall N=643	OSA N=417
Any AE	482 (75.0)	313 (75.1)
Any treatment-related AE†	[redacted]	[redacted]
Serious AE	27 (4.2)	21 (5.0)
Any treatment-related serious AEs†	[redacted]	[redacted]
AE leading to study drug/study discontinuation	59 (9.2)	36 (8.6)
Deaths	1 (0.2)‡	1 (0.2)‡

Adverse event	Patients receiving solriamfetol (all doses), n (%)	
	Overall N=643	OSA N=417
AEs occurring in ≥5% of patients (any treatment group)		
Headache	71 (11.0)	40 (9.6)
Nausea	57 (8.9)	31 (7.4)
Nasopharyngitis	54 (8.4)	35 (8.4)
Insomnia	51 (7.9)	35 (8.4)
Dry mouth	47 (7.3)	33 (7.9)
Anxiety	46 (7.2)	25 (6.0)
Decreased appetite	32 (5.0)	14 (3.4)
Upper respiratory tract infection	32 (5.0)	22 (5.3)

Abbreviations: AE, adverse event; CSR, clinical study report; OSA, obstructive sleep apnoea; TONES, Treatment of Obstructive sleep apnoea and Narcolepsy Excessive Sleepiness.
All AEs are [redacted]† Related or suspected related to study drug.
‡ Due to sepsis.
Source: Malhotra 2019 (102); CSR Table 29 (101).

Table 22: TONES 4: Summary of adverse events (Safety Population)

Adverse event, n (%)	Titration phase, Combined solriamfetol N=174	Stable-dose phase, combined solriamfetol N=157	Withdrawal phase	
			Placebo N=62	Combined solriamfetol N=62
Any AE	85 (48.9)	16 (10.2)	6 (9.7)	18 (29.0)
Any treatment-related AE†	[redacted]	[redacted]	[redacted]	[redacted]
Any serious AE	0	0	0	0
AE leading to study drug or study discontinuation	6 (3.4)	0	0	0
Deaths	0	0	0	0
AEs occurring in ≥5% of patients (any treatment group‡)				
Headache	17 (9.8)	2 (1.3)	NR	NR
Dry mouth	12 (6.9)	1 (0.6)	NR	NR
Nausea	12 (6.9)	1 (0.6)	NR	NR
Dizziness	10 (5.7)	3 (1.9)	NR	NR
Insomnia	10 (5.7)	1 (0.6)	NR	NR
Palpitations	8 (4.6)	1 (0.6)	NR	NR
Anxiety	7 (4.0)	1 (0.6)	NR	NR
Dyspepsia	4 (2.3)	0	NR	NR
Diarrhoea	4 (2.3)	0	NR	NR

Adverse event, n (%)	Titration phase, Combined solriamfetol N=174	Stable-dose phase, combined solriamfetol N=157	Withdrawal phase	
			Placebo N=62	Combined solriamfetol N=62
Nasopharyngitis	NR	NR	0	3 (4.8)
Aphthous stomatitis	NR	NR	0	1 (1.6)
Upper respiratory tract infection	NR	NR	0	1 (1.6)
Cough	NR	NR	0	1 (1.6)

Abbreviations: AE, adverse event; CSR, clinical study report; NR, not reported; TONES, Treatment of Obstructive sleep apnoea and Narcolepsy Excessive Sleepiness.
All AEs [redacted]† Related or suspected related to study drug.
‡ Any of solriamfetol 75-, 150- or 300 mg groups or placebo.
Source: Strollo 2019 (105); CSR Table 14.3.1.1.1a and Table 14.3.1.1.1b (104).

B.2.10.2 AE profile in placebo-controlled trials

- Based on the TONES 3 12-week placebo-controlled study, more patients experienced at least one AE with solriamfetol (67.9%) than with placebo (47.9%) (Table 20); most of these were dose dependent and more frequent with the unlicensed 300 mg dose compared to the other doses.
- The most frequent AEs (≥5% of patients in any treatment group, including the unlicensed 300 mg group; Table 20) with a higher incidence within the solriamfetol combined group compared with placebo included headache (10.1%), nausea (7.9%), decreased appetite (7.6%), anxiety (7.0%), and diarrhoea (4.8%), dry mouth (4.5%), insomnia (4.2%) and feeling jittery (3.9%).
- The majority of these AEs occurred within the first two weeks of initiating treatment, and resolved for the majority of patients with a median duration of less than two weeks.
- Serious AEs occurred less frequently with solriamfetol (0.8%, n=3), compared with placebo (1.7%, n=2), were not considered by the investigator to be related to study medication and showed no obvious pattern or trend.
- AEs that led to drug and/or study discontinuation were reported in 5.2, 3.2, and 4.3% of the solriamfetol 37.5, 75 and 150 mg arms, respectively, compared with 3.4% 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.
- In TONES 3, insomnia was reported in 1.7%, 0%, and 2.6% of patients receiving solriamfetol 37.5, 75, and 150 mg, respectively, compared with 1.7% of placebo patients; no patients discontinued due to insomnia[n].
- Events of insomnia were [redacted], across all the OSA trials (TONES 3–5).
- Furthermore, overnight PSG measurements, including total sleep time, number of awakenings, or wake after sleep onset did not reveal any statistically significant or clinically meaningful changes with solriamfetol compared with placebo after 12 weeks of treatment (TONES 3).
- In TONES 4, [redacted]
- An analysis of change performed for all PSG assessments found [redacted].

B.2.10.3.2 Suicidal ideation

- Depression is a common comorbidity in OSA (126), and the potential for depression and suicidality was explored in Phase 3 studies with the validated Columbia-suicide severity rating scale (C-SSRS) and a medical review of AEs.

[n] One patient receiving the unlicensed 300 mg dose discontinued due to insomnia

- However, in TONES 3 [redacted]
- Similarly, the C-SSRS did not reveal a pattern of suicidal ideation or suicidal behaviour related to solriamfetol across TONES 3–5, with findings reported for suicidal ideation on the C-SSRS similar to that of the placebo arm of TONES 3 placebo n=2, 1.7% compared with n=0 for solriamfetol); there were no reports of suicidal behaviour using the scale.

B.2.10.3.3 Risk for cardiovascular events, and BP and HR increases

- The most common cardiovascular AE in solriamfetol patients in TONES 3 was chest discomfort ([redacted]. The incidence of other cardiovascular AEs (>1%) included palpitations ([redacted], hypertension ([redacted] and BP increased ([redacted]). The corresponding rate in the placebo arm for each of these AEs was 0%.
  - The rates of these cardiovascular AEs related/suspected to be related to study drug were: chest discomfort ([redacted]), palpitations ([redacted]), hypertension ([redacted]), and BP increase ([redacted]).
- The overall incidence of hypertension/BP increase and tachycardia/HR increase in TONES 3 was low (n=10, 2.8%, and n=[redacted], [redacted]%, respectively) and all cases were mild (n=[redacted], respectively) or moderate (n=[redacted], respectively) in severity.
- These effects on BP and HR were anticipated based on the mechanism of action of solriamfetol, and the majority of events (n=[redacted]) occurred at the higher 150 mg or (unlicensed) 300 mg solriamfetol doses.
- There were small mean changes in BP and HR from baseline to week 12 (averages across the day from pre-dose to 9 hours post-dose) (Table 23) and the change versus baseline was greatest for the (unlicensed) 300 mg dose.
- These absolute changes from baseline in systolic BP and diastolic BP were lower than absolute changes reported in habitual coffee drinkers one hour after caffeine intake, as reported by Corti 2002 (systolic BP: +2.3 mm Hg; diastolic BP increase: +0.7 mm Hg) (127).

Table 23. TONES 3: change* from baseline to week 12 in BP or HR (Safety Population)

	Placebo	Solriamfetol 37.5 mg	Solriamfetol 75 mg	Solriamfetol 150 mg	Solriamfetol 300 mg
Mean (95% CI) change from baseline to week 12, as measured on MWT days*					
n	99	49	53	103	91
HR, bpm	0.1 (-0.9, 1.1)	0.7 (-1.3, 2.7)	0.8 (-0.8, 2.3)	2.2 (1.0, 3.4)	2.9 (1.7, 4.1)
Systolic BP	-0.2 (-1.7, 1.4)	1.8 (-0.6, 4.1)	0.5 (-1.8, 2.8)	0.7 (-0.8, 2.1)	2.5 (0.4, 0.6)
Diastolic BP	0.0 (-0.9, 1.0)	0.6 (-0.7, 2.0)	-0.2 (-2.0, 1.5)	0.5 (-0.5, 1.6)	1.5 (0.3, 2.7)
Mean (SD) change from baseline to week 8, as measured by ambulatory BP monitoring†					
n	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
HR, bpm	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Systolic BP	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Diastolic BP	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: BP, blood pressure; bpm, beats per minute; CI, confidence interval; HR, heart rate; SD, standard deviation; TONES, Treatment of Obstructive sleep apnoea and Narcolepsy Excessive Sleepiness.
Analysis among 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

- Long-term results from TONES 5 showed no clinically relevant changes in BP or HR from baseline of the parent study, [redacted] treatment (including the unlicensed 300 mg dose).
- Most events were mild or moderate in severity; none were serious, and the majority occurred at the unlicensed 300 mg dose.
- The majority of patients who experienced an AE of hypertension/BP increase had a history of BP increase or hypertension, and as observed in TONES 3, categorical increases in vital signs was highest for the (unlicensed) 300 mg dose.
- Serious AEs of a cardiovascular or potentially cardiovascular nature did not occur in TONES 3 and only occurred in TONES 5, but were uncommon and most frequently occurred at the (unlicensed) 300 mg dose:
  - 75 mg dose: [redacted] non-cardiac chest pain
  - 150 mg dose: [redacted] chest pain and cerebrovascular accident
  - 300 mg dose (unlicensed): 2 cases of atrial fibrillation, and [redacted] of acute myocardial infarction, angina pectoris, chest discomfort and pulmonary embolism

- In light of these effects appropriate precautions for solriamfetol use are listed in the SmPC (Appendix C), 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.

B.2.10.4 Abuse potential

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 (128) in which solriamfetol was compared with placebo and the amphetamine stimulant phentermine), indicated solriamfetol has low potential for abuse. Solriamfetol therefore has robust and sustained efficacy in treating EDS in OSA, balanced with low potential for AEs and low potential for abuse.

B.2.10.5 Other findings

B.2.10.5.1 Withdrawal effects

During TONES 4, in which patients on a stable dose of solriamfetol were then randomised to either continue solriamfetol or 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

Clinical experience demonstrated solriamfetol to be consistently well tolerated in both short- (6–12 weeks) and long-term (40–52 weeks) trials. The safety profile of solriamfetol has been well characterised and AEs are consistent with the pharmacology of the drug and similar to that observed in studies with solriamfetol in other populations. As outlined above, AEs are generally dose-related in frequency, mild or moderate in severity, occur within 2 weeks of initiating treatment and resolve for the majority of patients. The nature of the AEs is such that they can be detected, monitored, and managed with routine measures and treatments used in clinical practice, or if needed, addressed through dose reduction or drug discontinuation, as described in the SmPC (Appendix C).

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

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 Phase 2 study of solriamfetol in patients with OSA (Study 15-004; NCT02806895) but this study is not expected to provide any additional evidence of relevance to this submission within the next 12 months.

B.2.12 Innovation

In the UK, solriamfetol represents the only treatment option licensed and indicated for the management of EDS in patients with OSA. Although modafinil was previously licensed for the treatment of EDS in OSA, the EMA removed this indication in 2010 after a review procedure concluded that the benefits of modafinil do not outweigh the risks in the OSA population. Based on a Sleep Services Analysis[o] on the clinical management of EDS due to OSA in the UK, off-label modafinil is only used in very rare and exceptional circumstances to treat EDS due to OSA and cannot be considered routine practice (90).

The clinical trial programme for solriamfetol demonstrates the efficacy of solriamfetol in reducing sleepiness and improving wakefulness in patients with EDS due to OSA, whose EDS is not satisfactorily managed using a primary OSA therapy such as CPAP. In addition to its clinical efficacy in treating EDS, solriamfetol delivers additional health-related benefits that are not captured in the QALY calculation (presented in Section B.3).

[o] 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 OSA and the potential place in therapy of solriamfetol (90).

Solriamfetol addresses a substantial unmet need in clinical practice

In current UK clinical practice, there are no licensed treatments available that are specifically indicated for EDS due to OSA. Given the significant negative impact on daily life that patients with EDS due to OSA experience (Section B.1.3), this persistent EDS represents a substantial detriment in the daily life of these patients. The introduction of solriamfetol offers a new treatment option for patients with OSA whose EDS is not satisfactorily managed using a primary OSA therapy, and thus may contribute towards improved QoL in this patient population. There is limited literature specifically investigating the impact of EDS due to OSA (in isolation from the underlying OSA itself), however, based on the detriment associated with EDS prior to OSA diagnosis, it can be assumed that patients who do not achieve normalisation of EDS with a primary OSA therapy, similarly do not fully achieve the benefit to QoL improvements with this therapy. As such, these patients tolerate a level of QoL that cannot improve, due to the lack of available treatments for their EDS. The addition of solriamfetol to UK practice offers an effective and sustained treatment to manage EDS and thus improvements in function, ability to conduct usual activities and the ability to achieve high levels of work productivity in these patients (Section B.2.6.1.10).

Solriamfetol offers convenient dosing and extended duration of effect

Solriamfetol is a once daily, oral treatment, taken with or without food upon awakening. As mentioned above, patients with OSA may be taking treatments for multiple comorbidities, thus a once daily treatment can be easily added to an existing drug regimen. In addition to the once daily dosing, the beneficial effects of solriamfetol in treating EDS are observed within 1 week of treatment initiation and are sustained throughout the day. Therefore solriamfetol may deliver rapid and sustained reduction of the burden of EDS due to OSA; this is associated with rapid improvements in patient function and ability to conduct usual activities (Section B.2.6.1.5.1), which may in turn improve the QoL of their partner (Section B.1.3). In the proposed population for solriamfetol treatment (patients with EDS due to OSA whose EDS is not satisfactorily treated by a primary OSA therapy), the once daily dose represents a minimal change to their daily routine; this convenience combined

with the rapid and sustained solriamfetol efficacy offers a simple and effective treatment to manage EDS due to OSA.

Solriamfetol improves patient productivity at work and outside work

People with EDS experience significantly greater impairment in their work productivity and usual activities outside work, compared with people without EDS; additionally, when EDS is a symptom of an underlying condition (such as OSA) the level of impairment increases even further, compared with people without any underlying conditions and people with an underlying condition but who do not have EDS (30). EDS associated with OSA can have a substantial negative impact on a patient's life, and impair their ability to function and perform daily activities (52, 126, 129, 130). The impact of solriamfetol on work productivity and activity impairment was assessed in TONES 3 and TONES 5, using the WPAI:SHP questionnaire. In TONES 3, 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 $p<0.05$) (Section B.2.6.1.11). Long-term treatment with solriamfetol in TONES 5 (combined arm, including unlicensed 300 mg dose), led to reduced rates of presenteeism (impairment while working), overall work impairment and activity impairment outside of work by ≥25% from baseline in patients with EDS due to OSA; improvements were observed by week 14 and maintained throughout the study (up to 52 weeks) (Section B.2.6.2.2.4). This positive impact of solriamfetol on work productivity may provide an additional impact on QoL not captured in the QALY calculations, as solriamfetol may subsequently help patients who were previously unable to work due to their EDS, to enter/return into employment and subsequently increase their earning potential and/or their career prospects, in particular for those in low paid jobs. This increase in economic status may consequently positively impact the patient's family, their partner, and their mental health status if they were anxious or depressed about their reduced working capacity due to EDS; given that EDS due to OSA is also known to affect the partner's QoL and impact patient-partner relationships (Section B.1.3), there may additional benefits in QoL beyond the QALY due to the improved patient and partner QoL, and their improved relationship status, as a result of solriamfetol for the management of the EDS due to OSA (94).

Solriamfetol treatment does not modify sleep architecture

Insomnia is a common and expected side effect of wake-promoting treatments, based on the pharmacology of these drugs (131-133). Despite this, reported rates of insomnia in patients treated with solriamfetol in TONES studies was similar to that reported with placebo. 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, TONES 3 demonstrated that solriamfetol treatment was associated with low rates of insomnia (1.7% for combined solriamfetol 37.5, 75 and 150 mg doses, compared with 1.7% for placebo) and that no patients discontinued solriamfetol treatment due to insomnia (Section B.2.10.3.1).

Solriamfetol has a selective mechanism of action

Solriamfetol acts as a selective dual reuptake inhibitor of the wake-promoting neurotransmitters dopamine and noradrenaline (134) and these mechanistic characteristics are hypothesised to account for the robust wake-promoting effects of solriamfetol (135). 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, which is beneficial given that the OSA patient population is likely to be receiving treatment(s) for multiple comorbidities. 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 (Appendix C).

Solriamfetol has low abuse potential

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 (128)), 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 (Section B.2.6.2.3).

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 OSA (TONES 3, TONES 5 and supporting study TONES 4) shows that the effects of solriamfetol treatment on EDS due to OSA are clinically meaningful, rapid in onset (within 1 hour of dosing), and are maintained long-term with continued treatment (for at least 6 months[p]). In the trials, the clinical benefits of solriamfetol were demonstrated using validated subjective and objective outcome measures, including ESS, MWT, PGI-c or CGI-c. These efficacy results combined with the well-characterised safety profile of solriamfetol demonstrate its potential to improve the current treatment landscape for patients with EDS due to OSA.

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

TONES 3 is the pivotal RCT providing evidence of comparative efficacy of solriamfetol compared with placebo in adult patients with EDS due to OSA (diagnosed according to the ICSD-3 criteria). Patients were required to have EDS as demonstrated by a baseline ESS score ≥10, and an inability to stay awake as demonstrated by a baseline mean sleep latency of <30 minutes (the mean of the first four trials of a five-trial MWT), respectively.

Solriamfetol reduced EDS and improved wakefulness as demonstrated respectively by significant decreases in subjective ESS score from baseline to week 12 (LS mean difference vs placebo -1.9, -1.7 and -4.5, for solriamfetol 37.5, 75 and 150 mg respectively; all $p<0.05$), and significant increases in the duration of objective MWT mean sleep latency score from baseline to week 12 (LS mean difference vs placebo 4.5, 8.9 and 10.7, for solriamfetol 37.5, 75 and 150 mg respectively; all $p<0.01$).

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

Improvements in ESS versus placebo were observed from week 1 (the first measurement time point) ($p<0.001$ for solriamfetol 150 mg, $p<0.05$ for solriamfetol 75 mg and 37.5 mg). Normal ESS (≤10) scores (Table 6) were achieved by 51.8%, 55.2% and 70.7% of patients receiving solriamfetol 37.5, 75 and 150 mg doses respectively, compared with 37.7% in the placebo group. Further, evaluation of MWT demonstrated that patients achieved significant improvements at week 1 when receiving solriamfetol 75 mg ($p<0.05$) and 150 mg ($p<0.001$) doses, with numerical improvements observed at the 37.5 mg dose. 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 37.5, 75 mg and 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.

The improvements in the co-primary outcomes of ESS and MWT were associated with patient-reported improvements in overall condition, as reported using PGI-c; 55.4–89.7% of patients receiving solriamfetol 37.5–150 mg reported an improvement on the PGI-c compared with 49.1% of those receiving placebo. Patient QoL scores were also improved, as measured using the FOSQ-10 and SF-36v2; solriamfetol 150 mg delivered significant improvements compared with placebo in patient functioning at week 12 (using FOSQ-10; $p<0.05$) and on both the physical and mental component summary scores of the SF-36v2 (both $p<0.05$) compared with placebo. Furthermore, solriamfetol 150 mg delivered significant changes on the role physical, general health, vitality, social functional and role emotion domains of the SF-36v2 at 12 weeks, compared with placebo; numerical but non-significant improvements were observed for all other doses.

Improvements observed with EQ-5D were more limited showing no meaningful trends on either the EQ-5D Index or VAS scores; the lack of meaningful trends in EQ-5D scores in the OSA population is of uncertain cause, however at baseline, [redacted] of patients in TONES 3 had utility scores ≥0.9, and therefore reported no disutility due to their condition (Section B.3.4 for detail). Furthermore, at baseline in TONES 3, 90.5% of patients were rated by clinicians (using the CGI-s) as being at least moderately ill, however these patients had limited disutility on EQ-5D (mean index scores 0.8–0.84 for solriamfetol, compared with 0.85 for placebo). These baseline characteristics are inconsistent with the widely accepted negative impact of EDS and OSA on QoL (Section B.1.3), and suggest that the generic EQ-5D data collected in TONES 3 did not accurately reflect the substantial burden to QoL expected given the high burden of illness in these patients. Further discussion on the suitability of EQ-5D in the OSA population and relevance to economic modelling is discussed in Section B.3.4.

TONES 3 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 $p<0.01$).

B.2.13.1.2 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 OSA or narcolepsy who had previously completed a clinical trial for solriamfetol in EDS were enrolled; for patients with OSA these trials included TONES 3, as well as TONES 4 and Study 15-004). 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 (week 14) through to the final evaluation indicating that in addition to the effect on ESS, solriamfetol-induced improvements in QoL are maintained 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 OSA (as measured using the WPAI:SHP).

B.2.13.1.3 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 OSA; [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 a [redacted] for solriamfetol [all doses] vs placebo at the end of withdrawal phase in the overall and OSA populations).

B.2.13.1.3.1 TONES 4: Supporting Phase 3 comparative efficacy over 12 weeks

The comparative evidence from TONES 4 is consistent with that observed in the Phase 3 TONES 5 study and supports the comparative efficacy of solriamfetol compared with placebo in adult patients with EDS due to OSA. Solriamfetol significantly reduced sleepiness and increased the ability to maintain wakefulness in

patients with EDS due to OSA. Results from the randomised withdrawal phase demonstrated reversal of solriamfetol efficacy when patients discontinued treatment, and patients receiving placebo experienced a worsening of EDS to beyond the normal range (i.e. scores ≥10) but patients receiving solriamfetol maintaining their treatment efficacy.

B.2.13.1.4 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 OSA, as well as more broadly in patients with narcolepsy 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 mild to moderate, and dose-related, with highest rates associated with the 300 mg doses (unlicensed), mainly occur within 2 weeks of treatment onset and appear to be reversible. The majority of AEs were mild or moderate in severity (94.6% in TONES 3), and the nature of the AEs is such that they can be detected, monitored, and managed with routine measures and treatments used in clinical practice, or addressed through dose reduction or drug discontinuation (Appendix C).

In TONES 3, more patients with OSA receiving solriamfetol experienced at least one AE (37.5 mg, 63.8%; 75 mg, 48.4%; 150 mg, 70.9%) compared with placebo (47.9%). The most frequent AEs (≥5% of patients) included headache, nausea, decreased appetite, nasopharyngitis, and diarrhoea (Table 20). AEs that led to study drug and/or study discontinuation were reported in 5.2, 3.2 and 4.3% of the solriamfetol 39.5, 75 and 150 mg arms, respectively compared with 3.4% 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 3 were low (37.5 mg, 1.7%; 75 mg, 0.0%; 150 mg, 2.6%), and similar to placebo (1.7%). All events 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=1 in TONES 3; [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 OSA, and patients with OSA and EDS are more likely to be depressed than those with OSA but without EDS (32, 126, 130). The occurrence of depression and the risk of suicidality were therefore assessed in the clinical trial programme for solriamfetol in EDS due to OSA; AEs associated with depression were uncommon, and [redacted].

Due to the nature of their underlying OSA, patients with EDS due to OSA may have cardiovascular comorbidities (32-34), thus it is important that any wake-promoting agent for managing EDS does not induce or exacerbate any pre-existing cardiovascular conditions. Cardiovascular AEs (Section B.2.10.3.3) including palpitations, non-cardiac chest pain, BP increase, HR increase and tachycardia occurred at low rates (7.6% including the unlicensed 300 mg dose compared with 4.2% excluding the 300 mg dose. Serious AEs of a cardiovascular or potentially cardiovascular nature did not occur in TONES 3, and in TONES 5 were uncommon and most frequently occurred at the (unlicensed) 300 mg dose. Small mean increases in BP and HR were apparent from baseline to 12 weeks of solriamfetol treatment in TONES 3 (Section B.2.10.3.3); the effects on BP and HR were dose dependent and were greatest in the (unlicensed) 300 mg dose. Evidence from TONES 5 (including 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. Furthermore, although not directly comparable, the absolute changes from baseline observed in systolic BP and diastolic BP observed in TONES 3 were lower than the absolute changes reported in habitual coffee drinkers one hour after caffeine intake, (systolic BP: +2.3 mm Hg; diastolic BP increase: +0.7 mm Hg), and

substantially lower than the absolute changes reported for non-habitual coffee drinkers (systolic BP: +12.6 mm Hg; diastolic BP increase: +7.1 mm Hg) (127).

B.2.13.1.5 Conclusion

Solriamfetol is a wake-promoting agent that 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 practice.

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

The clinical trial programme for solriamfetol assessed EDS using validated objective and subjective outcome measures

The Phase 3 clinical trial programme for EDS in OSA included large, multinational and methodologically robust trials, that used validated well-recognised objective and subjective outcome measures to assess the efficacy and clinical benefits of solriamfetol for treating EDS in patients with OSA (TONES 3 and TONES 4) or patients with OSA or narcolepsy (TONES 5).

TONES 3 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 3 study, TONES 4 was a multicentre, methodologically robust, double-blind, randomised, placebo-controlled study, to assess the safety and efficacy of solriamfetol, and supports the evidence provided for TONES 5, that solriamfetol discontinuation is associated with loss of treatment efficacy but without rebound hypersomnia or withdrawal-related AEs.

The study populations were well balanced across treatment arms

The baseline demographics and disease-specific characteristics were similar across all three trials (TONES 3, TONES 5 and TONES 4), 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.

The trial comparator (placebo) was reflective of clinical practice in the UK, where no other treatments are licensed and indicated for EDS due to OSA

The inclusion of a placebo control group in TONES 3 was used to provide a robust assessment of the efficacy and safety of solriamfetol as a new investigational medicinal product. As solriamfetol is the only pharmacological treatment currently licensed in Europe to manage EDS due to OSA, the only comparator is placebo. 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' (136). 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 (136). TONES 5 and TONES 4 both included a randomised placebo-controlled withdrawal phase to assess the reversal of solriamfetol effects 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.

The patient demographics in the study populations were generally representative of the UK OSA population

TONES 3, 5 and 4 were large, multinational, well conducted and methodologically robust Phase 3 studies conducted in North America and Europe. Although these were multinational trials, there were no clinical sites in the UK.

In patients with OSA in TONES 3, TONES 5 and TONES 4, approximately [redacted]% were male, mean (SD) age was [redacted] years, median age was [redacted] years, and mean baseline ESS was 15–16, indicating high levels of EDS in these patient populations (Section B.2.6).

Information on the demographics of the OSA population in the UK is limited, however some detail is available from the 2013 British Lung Foundation (BLF) patient experience survey (n=2,671) (17), and the UK patients with EDS due to OSA (n=106) withthe EU5 NHWS analysis (Appendix M). In the BLF survey and NHWS analysis, 78% and 67% of the populations were male, respectively, which is slightly higher than the rate for TONES 3 (63%) but is reflective of the widely accepted higher prevalence of OSA in men. The mean age of patients in TONES 3 ranged from 54–57 years across treatment arms, consistent with the mean age of 53 years in the NHWS study, and the middle aged profile of patients in the BLF survey: 62% of participants were 50–69 years (mean age not reported). These values are also consistent with the expected middle aged profile of patients with OSA.

There is no information on the race distribution of patients with OSA in the UK, and neither the BLF survey nor NHWS analysis reported participant race, so it is unclear how the TONES trial data compares with the UK OSA population. Approximately 20% the patients in each of TONES 3–5 were Black/African American. As the TONES trials were predominantly based in the USA, this was likely driven in part by the higher proportion of the US population that identify as Black or African (13.4% per the US Census Bureau, 2018) (137), compared with the proportion of the UK general population who identify as Black (3.3% including Black African, Black Caribbean, and Black Other) per the 2011 census (138). There is limited evidence from the literature that Black patients with OSA have higher levels of EDS (defined by ESS scores) compared with White patients with OSA (139, 140), which may have increased the proportion of Black compared with White patients in a trial specifically targeting EDS due to OSA. No subgroup analysis between race was conducted as part of the trials, however there is no evidence to suggest that solriamfetol efficacy would be expected to differ between patients of different race.

In TONES 3, of patients using a primary OSA therapy at baseline, ~90% were using PAP (including CPAP), consistent with the 96% of the BLF Survey respondents who reported using CPAP. Furthermore, in TONES 3, the majority of patients (~70%) were using their PAP therapy to an optimal effective level (≥4 hours per night) consistent with usage in the BLF Survey: 91% of those using CPAP used it for

≥5 hours per night, and 56% for ≥7 hours per night. Compliance was not reported for the NHWS study.

The remainder of patients in TONES 3 were using oral devices or unknown devices, consistent with UK KOL Evidence that there are low rates of usage for alternative primary OSA therapies in the UK (51). In current practice oral appliances are not provided under NHS Dental Care (but are available privately), and are only appropriate in those with mild or moderate OSA (76). For each of the TONES 3–5 trials, a small proportion of the patients had a history of surgical intervention for the symptoms of OSA however in the UK surgery is typically reserved for severe cases (88, 90), therefore it would not be appropriate to compare the levels of surgery in the TONES 3 population to the levels observed in the UK.

As such, although information on the population demographic of patients with OSA in the UK are limited, and those with EDS due to OSA even more so, the evidence available from the BLF Survey and NHWS analysis indicates that the population in TONES 3 was similar to that in the UK OSA population in terms of age, gender and primary OSA therapy use

Trial populations compared with marketing authorisation and use in clinical practice

Both TONES 3, TONES 5 and supporting RCT TONES 4 provide evidence in patient populations relevant to the final NICE scope. The trials included patients with EDS due to OSA, who were using or had previously used a primary OSA therapy such as CPAP; this is consistent with the proposed positioning of solriamfetol in UK clinical practice and aligned with its indication:

> "Solriamfetol is indicated to improve wakefulness and reduce EDS in adult patients with OSA whose EDS has not been satisfactorily treated by primary OSA therapy, such as CPAP"

The proposed positioning of solriamfetol in UK clinical practice would be as an add-on treatment to standard of care (e.g. primary OSA therapy) in patients with OSA whose EDS is not satisfactorily managed by a primary OSA therapy. The trial populations (including patients who received the unlicensed 300 mg dose) are

consistent with this positioning in that the inclusion criteria required patients to be using or have previously attempted a primary OSA therapy.

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

TONES 3 covered the range of doses included in the licence for solriamfetol in OSA (37.5, 75 and 150 mg), and the use of this treatment in clinical practice in the UK. The doses were selected by randomisation thus no titration information is available. Based on the SmPC (Appendix C), the recommended starting dose in patients with OSA is 37.5 mg once daily, upon wakening. In TONES 4 and 5, solriamfetol titration was started at 75 mg and forced to the maximum tolerated dose, thus some patients may have been up-titrated based on good tolerability, but may not have required the higher dose from an efficacy perspective. As such, the dose split from the clinical trial programme for solriamfetol in OSA is unlikely to be fully reflective of the dose split that may be observed in clinical practice, where if a patient normalises on a particular dose, it is expected that the patient will remain on that dose. Data from the US suggest a [redacted] dose split for the 37.5, 75 and 150 mg doses of solriamfetol, respectively, but it is anticipated that UK prescribers will be more conservative than those of the US, and that in UK clinical practice, solriamfetol will have a 40/40/20 dose split.

The outcomes used in the trials are relevant to clinical practice in the UK

TONES 3, TONES 5 and TONES 4 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 (107, 108, 113-115).

Reductions of ≥3 points in the ESS score are considered clinically meaningful when assessing EDS (Table 6). However, UK KOL Evidence indicates that clinicians may accept variable levels of improvement, and/or any patient-reported improvement in condition as meaningful (51); in general, as long as the patient feels that treatment improves their condition, many clinicians will accept this to be a meaningful and effective response to treatment. In TONES 3, all solriamfetol arms (37.5, 75, 150 mg)

achieved a ≥3 point reduction in mean ESS scores (-5.0, -5.1 and -7.7 point reduction, respectively) after 12 weeks of treatment (Section B.2.6.1). Furthermore, in TONES 5, both groups receiving solriamfetol achieved a ≥3 point reduction in mean ESS scores after 2 weeks, maintained for up to 52 weeks (Section B.2.6.2).

The categorisation of EDS into mild, moderate, or severe based on ESS scores is common in the literature (20, 76, 87, 141, 142) but UK KOL Evidence suggests that it is rarely used in UK clinical practice (51). UK KOL Evidence further suggests that the use of ESS scores alone to assess improvements in EDS is highly variable, with many clinicians using a holistic approach, assessing patient-reported improvements to determine treatment response – i.e. it is the patient's reported reduction in the impact of EDS due to OSA on their daily function which is used to define a positive response. In situations where ESS is used to determine response, the absolute reduction in ESS required to define response varies widely, with some KOLs using an absolute reduction of 2–4 points but other KOLs reporting that any reduction is meaningful as long as the patient feels improved (51). Furthermore, based on this UK KOL Evidence, the MWT is rarely used in UK clinical practice for the assessment of EDS in patients with OSA. This is consistent with the results of a study that demonstrated [redacted]) (99). In TONES 5 and TONES 4, 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 (51).

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 (118), and would ordinarily be considered 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) (117). 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 (116, 143). 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 (116).

The EDS defined in the TONES studies are aligned with in boundary of ESS considered within the normal range in the UK population

In the UK, ESS scores ≤10 are considered 'normal' daytime sleepiness (Table 6), thus in clinical practice, patients with OSA would usually have ESS scores substantially in excess of 10 at treatment initiation. The eligibility criteria for TONES 3 included patients with ESS scores ≥10, thus a small proportion of patients in the trial had normal ESS values (ESS=10) at baseline: solriamfetol 37.5 mg, 5.4%; solriamfetol 75 mg, 5.2%, and solriamfetol 150 mg, 7.8%. However, the remove the variation between the clinical value (≤10) and the trial (≥10), for the purposes of the cost-effectiveness analyses (Section B.3) all analyses were conducted using individual patient level data (IPD) and patients with baseline ESS=10 were excluded such that the trial populations would more accurately reflect UK practice.

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 any published economic evaluations for interventions used in the management of EDS due to OSA that may inform the model in the current analysis. Although solriamfetol represents the only licensed treatment option for the management of EDS in patients with OSA whose EDS has not been satisfactorily treated by a primary OSA therapy, the inclusion criteria for the SLR covered studies for any pharmacological treatments (with or without CPAP). This included modafinil which is no longer licensed in this indication, and interventions used in other sleep disorders, such as narcolepsy. As anticipated, the SLR did not identify any economic evaluations for the cost effectiveness of pharmacological treatments, with or without CPAP, for managing EDS due to OSA. Full details of the SLR are presented in Appendix G, including a summary of the studies identified.

Due to the lack of identified studies in the SLR, an ad-hoc search of the NICE website was conducted to identify any relevant NICE TAs in this disease area that could inform the current modelling approach (Section B.3.2). There were no NICE TAs that assessed interventions specifically for EDS due to OSA, but the search identified one NICE TA “CPAP for the treatment of OSAHS”, hereafter TA139 (87). The focus of TA139 is CPAP for treating the underlying cause of OSAHS, however CPAP is the most widely used primary OSA therapy in the UK, and TA139 informs established clinical practice for CPAP treatment, thus the models available for this HTA were considered appropriate to inform aspects of the model in the current analysis (i.e. for the comparator: established clinical management without solriamfetol, as defined in the company decision problem, see Table 1).

Documentation for NICE TA139 describes two models:

- The model developed by the manufacturer, ResMed
- The model developed by the Assessment Group and subsequently published as a report, hereafter “McDaid 2007” (76)

A summary of the approach to modelling and model inputs used in the NICE TA139 HTA identified is provided in Table 24.

Table 24. Relevant NICE submissions

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 (76, 87) [*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 (76, 87) [*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 management of EDS in patients with OSA, versus "established clinical management without solriamfetol", the comparator in the company decision problem (Table 1).

A two-stage model was developed in Microsoft® Excel 2016, to model the outcomes (and associated costs) experienced by a patient cohort comprising adult patients with EDS due to OSA, over a lifetime time horizon. A decision tree reflected the first 12 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 built upon the approaches used in TA139 (87) by utilising IPD from the TONES 3 clinical trial to define responders and non-responders to treatment, allowing a robust comparative analysis and demonstrating the associated treatment-related changes in ESS scores.

The Assessment Group model from NICE TA139 accounted for the impact of EDS (as assessed using ESS) using a single EDS health state, which was linked to the specific primary OSA therapy being administered – this was modelled as a mean reduction from baseline in ESS and an associated impact on QoL. The use of a single treatment-associated health state assumed that for the duration of the analysis, all patients both remained on their primary OSA therapy (and accrued the associated costs) and achieved a stable level of ESS reduction. This modelling approach was appropriate when considering a primary OSA therapy to treat the underlying cause of OSA, because even if the primary OSA therapy did not completely resolve the patient's symptoms (such as EDS), the patient would continue using the primary OSA therapy to prevent recurrent apnoeic/hypopnoeic episodes during sleep and therefore avoid the long-term impact of OSA on their physical and mental health (Section B.1.3).

This modelling approach would not be appropriate for the current analysis, which describes the introduction of solriamfetol, the only licensed treatment option for the

management of EDS in patients with OSA whose EDS has not been satisfactorily treated by a primary OSA therapy. Firstly, in TA139, other than receiving a primary OSA therapy to treat the underlying OSA, there were no treatment options available specifically to manage EDS due to OSA therefore these patients were unable to achieve any ESS reductions beyond those achieved with primary OSA therapy; Conversely, in the current analysis, solriamfetol represents a treatment option that may reduce the patient's EDS further than is possible using only primary OSA therapy. Secondly, in clinical practice, some patients will respond to solriamfetol treatment, whereas a proportion of patients will not respond, therefore in the current analysis, applying a stable mean reduction in ESS across all patients would not adequately capture individual patient response. Finally, as described above, patients will continue using primary OSA therapy to treat their underlying OSA even if all of their symptoms of OSA (including EDS) have not been resolved, but in contrast, patients who receive solriamfetol to manage their EDS but do not respond, would discontinue solriamfetol as it makes neither clinical nor economic sense for these patients to continue solriamfetol treatment. In the context of solriamfetol treatment (as an add-on to continued standard of care), the use of a single treatment-associated health state is a limitation of TA139, and the current analysis aimed to address this by identifying responders and non-responders to solriamfetol treatment based on an absolute reduction in ESS (≥3 points), and subsequently continuing or discontinuing solriamfetol treatment accordingly. This approach avoids modelling the unnecessary use (and associated costs) of pharmacological therapy in patients who do not benefit from treatment.

To estimate the treatment effect for solriamfetol on EDS (as measured using ESS), the current model utilised IPD from patients with EDS due to OSA who were enrolled in the TONES 3 pivotal RCT for solriamfetol in OSA. In the UK, other than solriamfetol, there are no treatments specifically licensed and indicated to manage EDS due to OSA, thus the patients in the placebo arm of TONES 3 were receiving what can be described as 'established clinical management without solriamfetol' (as defined in the decision problem, Table 1), hereafter "standard of care without solriamfetol". As such, in the current analysis, the comparative effectiveness for

standard of care without solriamfetol was based on the placebo arm of TONES 3 (Section B.2.6.1).

As described above, the model for NICE TA139 assumed that patients receiving a primary OSA therapy maintained a stable level of EDS across the model duration, where the reduction of EDS attained was associated with the specific primary OSA therapy used. By applying this logic to TONES 3, it could be hypothesised that the level of EDS (as determined using ESS) would remain unchanged for the patients receiving standard of care without solriamfetol. However, using the placebo arm of TONES 3 to estimate the efficacy of standard of care without solriamfetol resulted in a proportion of patients achieving a clinical response in ESS, despite not receiving any active treatment. Although the placebo effect is common in RCTs, this effect would not be observed in clinical practice where these patients would not receive any treatment other than primary OSA therapy (as solriamfetol is the only treatment licensed and indicated to manage EDS due to OSA in the UK). To address this placebo effect, a centring exercise was performed to create a modified IPD (mIPD) population for use in the current analysis that removed the placebo effect (explained in detail in Section B.3.3.2). In performing the centring exercise, the underlying assumption of the models in TA139 (that ESS remains stable whilst on primary OSA therapy) remained true in the current analysis.

Although no formal treatment pathway exists in the UK for patients with EDS due to OSA, the model attempted to reflect the current management of patients based on UK KOL Evidence, which indicates that CPAP is the most widely used primary OSA therapy for patients with OSA (51). These KOLs further advised that there are no available, licensed, pharmacological treatments for patients with EDS due to OSA, whose EDS is not satisfactorily treated using a primary OSA therapy, and that reduction in ESS is an important clinical outcome in managing EDS due to OSA (51). Based on this evidence, the model focused on an absolute reduction in ESS scores as the measure of response.

The categorisation of patients into EDS severity scales as outlined by NICE Clinical Knowledge Summary (109): no EDS (ESS: 0-10), mild EDS (ESS: 11-14), moderate

EDS (ESS: 15-18), severe EDS (ESS: 18-24), was considered for health states in the current model, but was deemed inappropriate for several reasons:

- UK KOL Evidence suggests that in the UK clinicians rarely, if ever, categorise patients into mild, moderate or severe EDS, and do not use transitions across EDS categories to assess response to treatment (144), thus these definitions (mild, moderate, severe) were not included within the current submission (51).
- Although a reduction of 2–4 points in ESS is reported to be a clinically relevant change (110, 111), based on UK KOL Evidence achieving a pre-specified absolute reduction in ESS is not the only method for assessing treatment response - if the patient self-reports a positive impact of treatment on their EDS or daily function, in this situation, any ESS reduction is considered clinically meaningful (51).
- In light of the above feedback, there are a number of other limitations to utilisation of a health state model 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 were used to define health states within the current model, this would result in scenarios where patients were receiving and responding to treatment, but were not changing health state (and therefore were 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.

- In addition, the use of a health state model would require assumptions on the transitions between the various health states (both on- and off-treatment). In the absence of any such data, a more pragmatic approach was considered for the current model.

The current analysis therefore focused on identifying patients who had responded or not responded to solriamfetol treatment, by looking at the absolute reduction in ESS from baseline, irrespective of the baseline ESS score. For the purposes of the current analysis, response was defined as a ≥3-point reduction in ESS from baseline, the mid-point of the range cited in the literature (110, 111), with scores of 2 and 4 tested in scenario analysis. Although ESS scores ≤10 fall within the normal range for EDS, defining a response as 'normalised' would not reflect clinical practice. Based on UK KOL Evidence, a patient's self-reported improvement in condition, and/or a ≥3 point reduction in ESS is a clinically meaningful response to treatment (51). As such, a treatment response requirement of ESS ≤10 may prevent patients who have achieved meaningful responses outside this range from continuing treatment. Patients with higher baseline ESS scores are both more likely to benefit from any reduction in ESS scores, and are less likely to achieve normal ESS scores therefore a widely accepted value of ≥3 point reduction reflects an appropriate cut-off for response.

The models in TA139 incorporated patients' involvement in RTAs. There is an association between EDS and increased risk of RTAs (145), however in the UK, for patients with EDS due to moderate-to-severe OSA, ***or*** for patients with EDS due to mild or suspected OSA whose symptoms are uncontrolled after a period of ≥3 months, their OSA is considered a 'notifiable' medical condition by the DVLA, and they must surrender their driving licence (69). These patients must then meet the medical standards for driving before returning to driving, (control of condition, sleepiness improved, treatment adherence) although it is unclear exactly what the standards for re-starting driving entail (69, 146). Within the general population in the UK, the risk of being involved in an RTA is very small: the Department for Transport Reported road casualties in Great Britain 2018 Annual Report (147), 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 (148) and the risk of a car being involved 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*' which equates to a $3.7x10^{-6}$ risk of a car being involved in an RTA resulting in a casualty. Despite the evidence for an increased risk of RTA in patients with EDS due to OSA, due to the small risk of an individual in the general population being involved in an RTA, combined with both the stipulation that patients considered in the analysis (i.e. patients with EDS due to OSA) should not be driving due to their notifiable medical condition, and the evidence from TONES 5 that there were no AEs associated with motor vehicle accidents related to the study drug (102), this analysis assumed that the impact of RTA would be negligible and RTAs were consequently excluded from the current analysis.

The models for TA139 incorporated the possibility of cardiovascular events or strokes, by modelling the changes in systolic BP associated with the respective treatments, using the Framingham risk equations (76, 87). 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 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 and in the ERG report for NICE TA ID1602 (solriamfetol for treating EDS caused by narcolepsy), the impact of solriamfetol on systolic BP is minimal/negligible, therefore it was assumed that modelling cardiovascular events and stroke would have a negligible impact on the analysis and were excluded from the current analysis.

B.3.2.1 Patient population

The current model included adult patients with EDS due to OSA (diagnosed according to the ICSD-3 as per the TONES 3 eligibility criteria; Table 4), with EDS defined as a baseline ESS score >10 (107). This is consistent with the population defined in the NICE scope (Table 1), and broadly consistent the TONES trials

(Section B.2.6.1, B.2.6.2, and B.2.6.3), and the European marketing authorisation of solriamfetol (Appendix C), both of which defined EDS as ESS ≥10.

As the TONES studies included patients with ESS scores ≥10, a small proportion of patients had normal ESS values (ESS=10) at baseline (solriamfetol 37.5 mg, 5.4%; solriamfetol 75 mg, 5.2%; solriamfetol 150 mg, 7.8%). For the purposes of the current analysis, an EDS definition of ESS >10 was assumed, thus all patients with a baseline ESS=10 were excluded from the TONES 3 IPD utilised in the model.

The demographics and baseline disease characteristics of the model cohort were based on the patient population of TONES 3, however for the reasons outlined above, patients with a baseline ESS=10 were excluded. Key baseline characteristics of the model cohort are described in Table 25. The mITT population (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 MWT or ESS) was used for the model cohort as this was consistent with the population used to analyse the co-primary efficacy endpoint of ESS in the trial (Table 10).

Information on the demographics of the OSA population in the UK is extremely limited and restricts the ability to make comparisons between the trial population and the population of patients with OSA in England. However, within the trial, patients were middle aged, primarily male, and the majority of those who were using a primary OSA therapy were using PAP, consistent with the widely accepted position of CPAP as the first-line therapy for the underlying cause of OSA in the UK.

Table 25. Patient populations included in the economic model

Baseline characteristics	Overall TONES 3 population*	Overall TONES 3 (mITT)†	Solriamfetol†			Standard of care	Source
			37.5 mg	75 mg	150 mg		
Number of patients, n	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	TONES 3
Age, years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
Female, %	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
ESS score at baseline	[redacted]	[redacted]	[redacted]	[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
* Overall data includes patients for all doses, including the 300 mg dose.
† Excludes patients with an ESS=10 at TONES 3 baseline.

The model considered patients with OSA whose EDS is not satisfactorily managed using a primary OSA therapy, reflecting the proposed positioning of solriamfetol in UK clinical practice (Section B.1.1). This positioning is based on evidence from the Sleep Services Analysis which indicates that CPAP is an established first-line treatment for OSA in the UK (90) and the status of solriamfetol as the only licensed treatment option for the management of EDS in patients with OSA whose EDS has not been satisfactorily treated by a primary OSA therapy.

B.3.2.2 Model structure

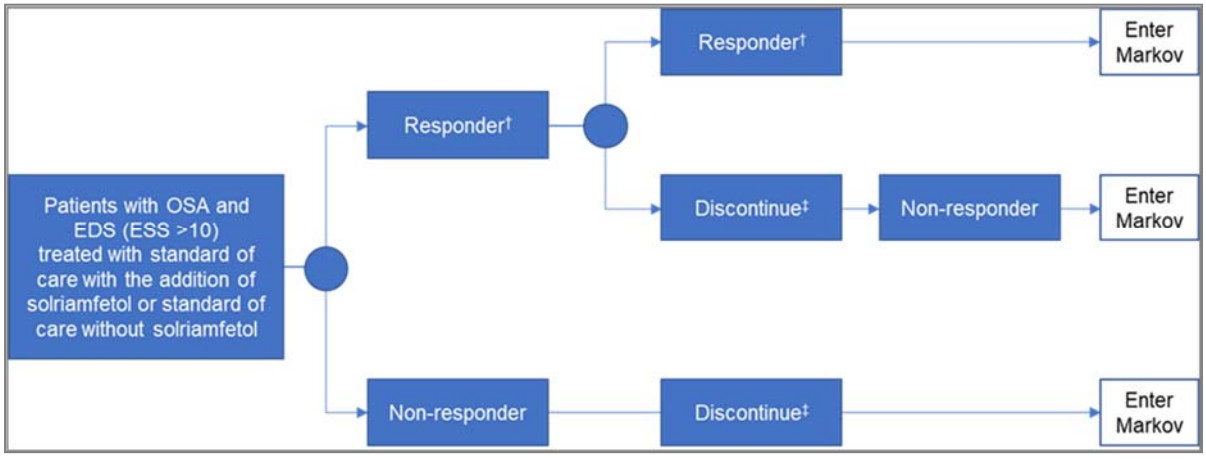
The current analysis used a two-stage model developed in Microsoft® Excel 2016 consisting of a decision tree that determined responder and non-responder status at 12 weeks of treatment, followed by a Markov model with annual cycles that estimated outcomes for each treatment over the remainder of the model lifetime time horizon. Patients were assumed to reach a final/stable dose of solriamfetol within the first 12 weeks of treatment, and responder and non-responder patients at 12 weeks, 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 12 onwards, and contained three health states: responder, non-responder, or death.

All patients entered the initial decision tree phase (Figure 16) with the same baseline ESS score, and received either standard of care with the addition of solriamfetol, or standard of care without solriamfetol. Patients were assumed to reach a final/stable dose of solriamfetol within the first 12 weeks of treatment, and were then classified as either “responders” or “non-responders” defined according to whether or not they achieved a ≥3-point reduction in ESS from baseline after 12 weeks of solriamfetol treatment (Section B.3.3.1). UK KOL Evidence indicates there is no consensus on when response to treatment would be assessed in practice (51), therefore the 12 week time point was chosen, based on the primary endpoint of TONES 3.

The patients who entered the response state were assumed to have both a reduction ESS score and the associated treatment cost, specific to the solriamfetol dose received, for as long as they remained on therapy. Patients receiving standard of care without solriamfetol were considered “non-responders” by default: they were assumed to maintain the stable level of ESS associated with their standard of care (as per the model in TA139) and they were not receiving any active treatment specifically for their EDS, thus were unable to achieve any change in ESS within the decision tree phase. This was achieved by modifying the TONES 3 IPD by conducting a centring exercise (further detail in Section B.3.3.2) on both arms to adjust for the placebo effect observed in the trial. Based on the timing of the first post-baseline ESS measurement within TONES 3, for the current analysis, the

treatment effect of solriamfetol on ESS was observed within 1 week of treatment initiation (Section B.2.6.1.6).

Figure 16. Treatment initiation (first 12 weeks) – Decision tree schematic



Abbreviations: EDS, excessive sleep disorder; ESS, Epworth Sleepiness Scale.
* Patients who received solriamfetol also received standard of care.
† A responder was defined as a patient achieving a reduction in ESS ≥3.
‡ Patients discontinued solriamfetol treatment but continued standard of care for the lifetime of the model.

Although the improvement in ESS occurred from the first week, and is reflected in the QALY calculations, 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 12. Patients were assumed to reach a final/stable dose of solriamfetol before this 12 week assessment. Due to the wide variability in clinical practice with regards time to follow-up described in the Sleep Services Analysis and UK KOL Evidence (51, 90), a response to treatment (≥3 point reduction in ESS from baseline) was assumed to be assessed at 12 weeks to reflect the timing of the co-primary endpoints of TONES 3 (Section B.2.6.1.2), although it is acknowledged that in clinical practice this may vary from 2 weeks to 3 months.

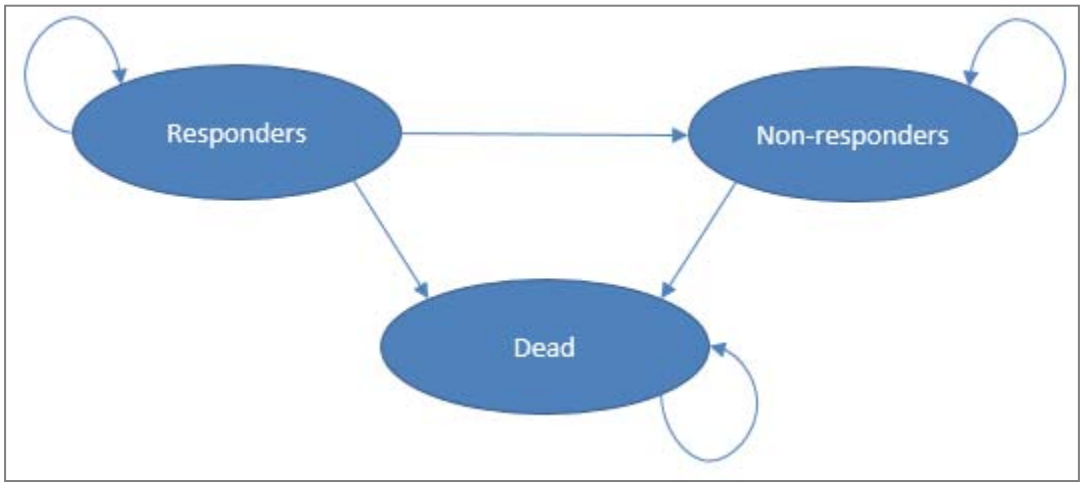
Although patients were categorised as responders and non-responders it should be noted that the relative level of response, as measured by reduction in ESS, varied for each treatment. The proportion of patients achieving response (≥3 point reduction in ESS from baseline), and the respective mean absolute reduction in ESS from baseline for responders and non-responders for each dose of solriamfetol was recorded and used to estimate the associated impact on QoL. As previously noted (Section B.3.2), based on the model approach in TA139, patients receiving standard

of care without solriamfetol were assumed to maintain a stable level of ESS (equivalent to a non-responder), thus the baseline ESS was used to estimate the associated QoL.

Following the 12-week decision tree phase, patients moved into a Markov phase (Figure 17) for the remainder of the model time horizon, with annual cycles. The model consisted of three mutually exclusive health states:

- Responders: on treatment for EDS with a maintained response (defined as the treatment-specific reduction in ESS).
- Non-responders: patients who have not achieved a response or have withdrawn from treatment for EDS due to AEs or loss of efficacy (returning to the mean baseline ESS).
- Dead: absorbing health state.

Figure 17. Maintenance treatment (12 weeks onward) – Markov Model schematic



OSA is a chronic condition, and in the absence of evidence to support any movement between the health states at a more granular cycle length, annual cycles were chosen. Half cycle correction was incorporated to address the long-cycle length, in line with the NICE reference case. Furthermore, evidence from patients who were enrolled into TONES 5, having previously completed TONES 4, suggests that following extended periods of solriamfetol discontinuation patients will revert to their baseline ESS score but not beyond their baseline levels (Section B.3.3.2 for further detail).

Long-term solriamfetol data from TONES 5 demonstrated that in the first year following solriamfetol initiation, the level of ESS improvement achieved remained relatively constant in responders to treatment. Although TONES 5 did not assess the solriamfetol 37.5 mg dose, the results for the 75 and 150 mg dose indicate that patients respond rapidly to solriamfetol and that once patients achieve a stable level of response, they will maintain this level of response long-term (for up to 1 year). The results from TONES 3 indicate that for all three doses (37.5, 75, 150 mg), patients respond rapidly to solriamfetol and maintain their response for up to 12 weeks (Section B.2.6.1), mirroring the results observed in TONES 5. As such, there is no reason to assume that the 37.5 mg dose would not follow a similar trend to that observed for 75 and 150 mg in TONES 5, therefore the current analysis assumed that solriamfetol 37.5 mg would maintain a stable level of response over the long-term.

As previously noted, the TA139 assessment assumed a constant effect of treatment over the respective model time horizons. Further, TONES 5 indicates there is no treatment waning with long-term solriamfetol treatment. Therefore, the current analysis assumed that unless they discontinued solriamfetol treatment due to lack of efficacy over time, or treatment emergent adverse event (TEAE), all responders to solriamfetol treatment remained in a response state, with the same treatment-adjusted ESS for the duration of the analysis.

As described in Section B.1.3, although other therapies may be considered, CPAP is the most widely used primary OSA therapy to manage the underlying OSA in the UK (51). In the BLF patient experience survey of patients with OSA, 96% of respondents were using CPAP (and 91% were using CPAP for at least five hours per night) (17). Based on evidence from the Sleep Service Analysis and UK KOL Evidence, up to 1/3 of patients will not respond to, or are intolerant of CPAP therapy; these patients who do not initially respond well to CPAP receive treatment adjustments such as mask fitting, or have their CPAP pressure adjusted and monitored until optimum pressure is achieved and the patient is as stable as possible (90). Alternatively, some of these patients may instead choose to use a mandibular device/oral appliance to treat their underlying OSA, or in severe and very limited cases, patients

may be considered for surgery (51, 90). There are no figures available regarding the frequency of use of these alternatives, but UK KOL Evidence indicates it is a very small minority. At this stage, these patients are considered to be receiving optimal effective treatment but it is important to understand that this “optimal effective treatment” refers to management of the underlying OSA. Although they are not specifically indicated to manage EDS, a primary OSA therapy (including CPAP) may resolve EDS in some patients with OSA, however for a proportion of patients, EDS is not satisfactorily reduced by their primary OSA therapy and these patients continue to experience the burden of their EDS. In the absence of any clinical evidence to demonstrate the relative efficacy or impact on EDS of the available primary OSA therapies in the UK, the current analysis considered the efficacy of standard of care without solriamfetol to be equivalent regardless of the type of primary OSA therapy being used by the patient.

Solriamfetol represents the only licensed treatment option for the management of EDS in patients with OSA whose EDS has not been satisfactorily treated by a primary OSA therapy. In current UK clinical practice there are no treatment options for this patient population, and standard of care (without solriamfetol) does not differ for patients with or without persistent EDS. Therefore, it is expected that solriamfetol will be prescribed independently of the patient’s standard of care (i.e. the patient’s ‘established clinical management without solriamfetol’ will continue regardless of the management of EDS). Based on this expectation, it was assumed for the current analysis that regardless of the type of primary OSA therapy being used for their standard of care, all non-responders to solriamfetol remained in the same health state and with the same level of EDS (i.e. maintained the health state they were in before solriamfetol initiation) for the duration of the analysis, reflecting previous assumptions in TA139.

B.3.2.3 Time horizon

OSA is a chronic condition, therefore this analysis assumed a lifetime horizon, in line with current NICE guidance (149). The model assumes an average starting age of [redacted] years, to reflect the mITT population from TONES 3, and the model considers a

time horizon at which all patients have died or are 100 years old. 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 (150) to estimate annual mortality rates. The model assumed no treatment-related impact on mortality.

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 (149). The impact of discounting at 0% and 6% was assessed in sensitivity analyses.

B.3.2.6 Model outcomes

The model outputs included the total costs and QALYs for each treatment, and the incremental values, allowing calculation of the ICER expressed as cost per QALY gained, only direct costs were included. LYs for each treatment were reported but as there was no assumption of a treatment-related impact on mortality, the number of LYs estimated remained the same for each treatment.

B.3.2.7 Comparison of the current analysis with previous appraisals

As described in Section B.3.1, the economic SLR identified a previous HTA for treatment of patients with OSA: NICE TA139 considered CPAP for the treatment of OSAHS (87). Solriamfetol is indicated to manage EDS in patients with OSA whose EDS is not satisfactorily treated by a primary OSA therapy. Solriamfetol is not a treatment for the underlying cause of OSA. A summary of the main characteristics and assumptions used within the model in TA139 and a comparison with the current analysis is provided in Table 26.

Table 26. Features of the current economic analysis

	Previous appraisals	Current appraisal	
Factor	**TA139 Assessment group model**	**Chosen values**	**Justification**
Time horizon	Lifetime	Lifetime	In line with the NICE Reference Case
Treatment waning effect	Not considered	Only treatment discontinuation due to lack of efficacy is incorporated using data from TONES 5; discontinuation due to waning is not included.	TONES 5 presents data directly relevant to the decision problem in terms of long term efficacy, and there is no evidence to suggest treatment waning based on this long-term data.
Source of clinical data	Pre- and post-treatment ESS scores from identified RCT data (151-154)	TONES 3	TONES 3 is the pivotal RCT for solriamfetol in treating EDS due to OSA as defined in the NICE scope.
Source of utilities	ResMed company submission: A before and after study (152) Assessment Group analysis: IPD from a clinical study mapping ESS to EQ-5D (155)	NHWS analysis mapping ESS to EQ-5D (Section B.3.4.2)	In the absence of suitable trial-based EQ-5D utilities from TONES 3, and consistent with the ESS to EQ-5D mapping algorithm developed by the Assessment group for TA139, a similar approach was taken. The NHWS was considered 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	Jazz Pharmaceutical solriamfetol price PSSRU 2019 (156)	Standard cost sources were used in line with the NICE Reference Case

Abbreviations: EQ-5D, 5 dimension EuroQoL; ERG, evidence review group; ESS, Epworth Sleepiness Scale; IPD, individual patient level data; 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; RCT, randomised controlled trial; TONES, Treatment of Obstructive sleep apnoea and Narcolepsy Excessive Sleepiness.

B.3.2.8 Intervention technology and comparators

Solriamfetol represents the only licensed treatment option for the management of EDS in patients with OSA whose EDS has not been satisfactorily treated by a

primary OSA therapy; solriamfetol is not a therapy for the underlying airway obstruction causing OSA (Appendix C). As such, this analysis assumed that solriamfetol is a new treatment option, specifically indicated to manage EDS due to OSA, that will be offered to patients who are receiving established clinical management of OSA.

The comparator in the current analysis was standard of care without solriamfetol, which was considered equivalent to established clinical management without solriamfetol per the company decision problem (Table 1).

The intervention in the current analysis was standard of care with the addition of solriamfetol. The doses used were those assessed in TONES 3, and per the European marketing authorisation (37.5, 75 and 150 mg; see Appendix C). The 300 mg dose of solriamfetol is unlicensed and was therefore excluded from the current analysis.

Table 27. Characteristics of treatment regimens for comparators included in the model

Intervention	Daily dose	Source
Standard of care with the addition of solriamfetol	Solriamfetol 37.5 mg qd, oral	Solriamfetol SmPC (Appendix C)
	Solriamfetol 75 mg qd, oral	
	Solriamfetol 150 mg qd, oral	
Standard of care without solriamfetol	Not applicable	Not applicable

Abbreviations: PAP, positive airway pressure; qd, once daily; SmPC, summary of product characteristics.

B.3.3 Clinical parameters and variables

The sections below present the sources of data that informed the rates of response and the relative impact on ESS for each treatment considered in the current analysis. The ESS was used as the main measure of EDS, consistent with its use as a co-primary endpoint in TONES 3 (Section B.2.6), and its frequent use in current clinical practice (51). In addition, ESS was the primary measure of EDS used in TA139 when considering EDS in OSAHS (76, 87). The MWT was considered as an alternative endpoint for the current analysis but based on UK KOL Evidence the MWT is rarely used in UK practice for the assessment of EDS in patients with OSA

(51), thus MWT was not included in the current analysis. Although MWT was not explicitly included in the current analysis for the reasons outlined above, the consistent response to solriamfetol observed in the MWT data from TONES 3 strengthens the overall economic case.

In TONES 3, the positive impact of solriamfetol treatment observed using the objective MWT, was consistent with the subjective ESS outcomes observed and therefore increases confidence that the significant treatment effects observed within the solriamfetol arms in TONES 3 are not simply a regression to the mean and will be achieved in clinical practice. Furthermore, as outlined in Section B.3.3.2, data from the subgroup of [redacted] This evidence combined with the positive impact on MWT indicates the results observed in TONES 3 are unlikely to be regression to the mean.

B.3.3.1 Clinical data: Timepoint of response assessment

According to the Sleep Services Analysis[o] there is wide variability in clinical practice with regards the intervals between follow-up visits – ranging from 4 weeks to 9 months, in some cases, due to limited capacity rather than clinical preference (90). In the absence of clearly defined time points in practice, the 12-week assessment in the current analysis reflects the clinical data from TONES 3 in which the primary endpoint was analysed at 12 weeks.

It was assumed that to achieve optimal dose titration, interim follow-up visits may occur during this 12-week period, for which the number of visits varied according to the final dose of solriamfetol selected. The current analysis assumed that at 12 weeks after solriamfetol initiation, all patients would be assessed for response by a specialist. In the base case, at 12 weeks, all non-responders to solriamfetol treatment (Section B.3.2.2) were assumed to discontinue therapy.

B.3.3.2 Clinical data: response for standard of care without solriamfetol

For the purposes of this analysis the placebo arm of TONES 3 was used to estimate the efficacy of standard of care without solriamfetol. However, this meant there was a proportion of patients achieving a model-defined response in ESS, despite not receiving an active treatment. Although the placebo effect is common in RCTs, in the UK solriamfetol represents the only treatment option licensed for the management of EDS in patients with OSA, therefore in clinical practice, patients with EDS due to OSA who are receiving standard of care (without solriamfetol) would not receive any treatment for their EDS, and would continue a primary OSA therapy for their underlying OSA. The response rate experienced by patients in the placebo arm posed a modelling challenge within the current analysis: what should happen when patients in the arm receiving standard of care without solriamfetol, 'stop treatment'? As they are not receiving any treatment specifically for the management of their EDS, they cannot discontinue "nothing". Therefore, a mechanism to adjust for the placebo needed to be implemented.

Three common placebo mechanisms are considered in the context of RCTs (157):

- ''regression to the mean'' – the effect arising from natural variation and the preferential selection of patients with acutely severe disease into clinical trials),
- "Hawthorne effect" – a patient expectancy effect specific to the clinical trial setting,
- "true placebo" – the patient expectancy effect generalisable to clinical practice.

Regression to the mean assumes that natural variation within the clinical trial may lead to a placebo effect. Typically, patients with acutely severe disease are recruited into trials, thus the trial population consists of patients who are currently experiencing a (potentially) temporary worsening in their condition. As a result, these patients are likely to experience improvement when disease severity is next measured, regardless of any treatment benefit, as they tend toward their individual mean state. Within the TONES trials, the assumption that any placebo effect is solely due to regression to the mean is considered to be extremely unlikely due to (i) the magnitude of the improvement of ESS experienced in all treatment arms, (ii) the stable effect observed in MWT scores across all timepoints and all arms in TONES 3

and (iii) the stable use of primary OSA therapy of TONES 3 patients at baseline. The patients enrolled into TONES 3 were required to have a stable level of primary OSA therapy for ≥4 weeks prior to the trial – furthermore, the patients who were compliant to this therapy can be considered effectively treated for their OSA (as demonstrated by mean AHI scores in the normal range) and by default are receiving optimal standard of care for their underlying condition. As such, these patients are not considered to be in a temporary severe state of disease and it is highly unlikely that regression to the mean would occur in this patient population.

Furthermore, evidence from patients who were enrolled into TONES 5, having previously completed TONES 4, [redacted]. The mean baseline ESS score in TONES 4 was 15.4; at the end of TONES 4 (after the two week randomised withdrawal phase), mean ESS scores were 6.4 for patients who had continued receiving solriamfetol during the withdrawal phase (n=60) compared with 10.8 for those receiving placebo (n=62).

A total of [redacted] patients from TONES 4 subsequently enrolled in TONES 5[q] and these patients had a mean ESS score of [redacted] at baseline. This indicates that over time, [redacted]. It is important to note that after restarting solriamfetol treatment within TONES 5, these [redacted] patients achieved a mean (SD) ESS score of [redacted] after two weeks of solriamfetol treatment, indicating that [redacted]. This data from TONES 4 provides evidence that regression to the mean is not occurring with solriamfetol treatment, and that the effects of solriamfetol on ESS reflect a true treatment-related efficacy.

[q] The proportion of patients from each arm who enrolled in TONES 5, and the duration of dose interruption between completing TONES 4 and initiating TONES 5 are unknown.

It is reasonable to assume that if the patients in TONES 3 were not being observed, their benefit from the placebo treatment would be reduced, but they would still gain a benefit to EDS purely due to the ritual of treatment administration (or placebo), thus the placebo effects observed in TONES 3 are more likely to be a "true placebo" effect than a "Hawthorne effect".

The difficulties with the outcome measure of ESS is that EDS is a less tangible disease factor compared with more objective measures used in other indications, e.g. cancer. In patients with cancer, tumour growth can be measured through imaging to provide an objective (or near objective) measure of the rate of tumour growth (in volume/mm^3). Less-tangible outcome measures (i.e. EDS) are more difficult to quantify and inherently more susceptible to the Hawthorne effect, as EDS is likely to have a behavioural component (158), whereas the rate of tumour growth would not. In this case, placebo-adjustment of the ESS scores from TONES 3 is a reasonable method of accounting for the trial-specific treatment effect observed in the placebo, as this approach assesses only the incremental improvements observed in the solriamfetol versus placebo arms.

The Hawthorne effect scenario was selected as the base case as it was deemed to the fairest assumption, and most conservative of the two remaining credible placebo mechanisms. The "true placebo" scenario may provide an overly favourable ICER for solriamfetol, as this approach reduces the placebo ESS effect to zero and assumes the treatment effect of solriamfetol is absolute. A 'True placebo' scenario is considered in Section B.3.8.4.3.

For the base case analysis, assuming the "Hawthorne effect" applied to TONES 3, a centring exercise was conducted on the IPD for TONES 3 to placebo-adjust both the solriamfetol and placebo arms. As a result of the centring exercise, all patients in the placebo arm remained at their baseline ESS for the duration of the model. In the solriamfetol arms, centring was performed by subtracting the mean baseline ESS *of the placebo arm* from each individual ESS record in the IPD *of the solriamfetol arms*, in a manner resembling a method typically applied in linear regression.

This centring exercise thus negated any Hawthorne placebo effect present in each arm due to the standard of care component in both arms, and allowed only the incremental benefits of solriamfetol on ESS to be modelled. This also removed the requirement to make any assumption(s) about the impact of standard of care on ESS after 12 weeks of treatment and for the remainder of the model time horizon. As the data were centred, discontinuation of solriamfetol was not considered within the standard of care without solriamfetol arm, as patients were not receiving any active treatment.

Prior to deciding upon the centring approach, two alternative approaches to placebo-adjustment using the MWT or PGI-c scores were considered. It was hypothesised that combining either one of these outcome measures with the ESS, to determine if patients were responders/non-responders to treatment, may have allowed for a placebo adjustment. However, the challenge remained in using either of these approaches that a proportion of patients receiving standard of care without solriamfetol would achieve a model-defined response (≥3 point reduction in ESS) despite not receiving any active treatment for the management of their EDS.

B.3.3.3 Clinical data: response for solriamfetol

Efficacy estimates (response) for solriamfetol were determined from the mITT Population IPD from the TONES 3 trial. The IPD provided the ESS score for each patient at baseline and at week 12, which allowed for the reduction in ESS to be determined for each patient. The base case analysis assumed that response was a reduction of ≥3 points in ESS from baseline to week 12 (110). Although ESS scores ≤10 are within the normal range, defining a response as ‘normalised’ or ESS ≤10 would not reflect clinical practice, where based on UK KOL Evidence, EDS is multidimensional and what is considered ‘normal’ depends on and is highly specific to the individual; KOLs report that the patient’s self-reported improvement in condition, and/or a reduction of 2–4 points in ESS reflects a clinically meaningful response to treatment (51). Based on this KOL evidence, the widely accepted value of ≥3 point reduction in ESS defined a response in the base case for the current analysis, with scores of ≥2 and ≥4 assessed in scenario analyses.

As described in Section B.3.2.1, the IPD from TONES 3 comprised all patients with a baseline ESS >10 (i.e. excluded patients with baseline ESS=10) and for those patients randomised to the licensed doses of solriamfetol (37.5, 75 and 150 mg), the mean (SD) baseline ESS for patients with ESS >10 at baseline was [redacted].

As described in Section B.3.3.2, the use of the placebo arm to estimate the efficacy of standard of care without solriamfetol led to a proportion of patients achieving a response, despite not receiving an active treatment. To address this, a centring exercise was conducted such that patients receiving placebo experienced no treatment effect and the ESS score for all patients receiving solriamfetol was reduced by the mean change in ESS within the placebo arm.

This approach reduced the efficacy of the solriamfetol arms in TONES 3 to account for the potential placebo effect and removed the modelling challenge associated with discontinuation within the standard of care without solriamfetol arm, which was not receiving active treatment. All subsequent analyses were therefore based on an mIPD dataset. Figure 18 depicts how the mIPD were split into responders and non-responders, and the respective mean reduction in ESS for each group at week 12. Note that the data did not follow a normal distribution; this curve is therefore purely illustrative.

Figure 18. Illustration of IPD for standard of care with the addition of solriamfetol

Abbreviations: ESS, Epworth Sleepiness Scale; IPD, individual patient level data.
Δ represents reduction 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 size for each solriamfetol dose in TONES 3, a scenario analysis utilising bootstrapping methods (as detailed by Gray 2010 (159)) to sample from the mIPD was conducted. The model drew a sample of 5,000 patients, with replacement, from the original mIPD and for each treatment arm within the analysis. The clinical output for each sample was then utilised in the model, and the associated costs and QALYs were recorded for all treatment considered. 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. For PSA, the model drew a sample of patients equal in size to the associated arm in TONES 3 (Section B.3.8.1).

B.3.3.4 Clinical data: change from baseline in ESS

At 12 weeks, the reduction in ESS from baseline was reported and averaged for all patients identified as responders or non-responders. This generated different reductions from baseline in ESS scores for responders and non-responders in the standard of care with the addition of solriamfetol and the standard of care without solriamfetol arms, and for each individual treatment (Table 28). As the QoL data was derived from the mean reduction in ESS for each treatment (Section B.3.3.1), the associated utility of responders and non-responders also varied according to the specific treatment received.

Table 28. Clinical data utilised in the current (OSA)

Product, daily dose	Proportion of responders (ΔESS from baseline ≥3)	Mean ESS in responders†	Mean ESS in non-responders†
Standard of care with solriamfetol 37.5 mg	[redacted]	[redacted]	[redacted]
Standard of care with solriamfetol 75 mg	[redacted]	[redacted]	[redacted]
Standard of care with solriamfetol 150 mg	[redacted]	[redacted]	[redacted]
Standard of care without solriamfetol	[redacted]	Not applicable*	[redacted]

Abbreviations: ESS, Epworth sleepiness scale; IPD, individual patient data; mIPD, modified individual patient data; OSA, obstructive sleep apnoea.
Δ represents the reduction in ESS from baseline.
* Due to the centering exercise conducted to adjust for the placebo effect (Section B.3.3.2), there were no responders in the standard of care without solriamfetol arm by default.
† Change estimated via mIPD.

Consistent with evidence from TONES 3 (Section B.2.6.1.2), the base case analysis assumed that reduction in ESS occurred after 1 week of treatment and that the treatment response would be assessed clinically at week 12; for responders, the effect on ESS persisted for the duration of the model time horizon as long as the patient remained on therapy.

Based on these parameters, all non-responders were assumed to experience any changes in ESS they achieved within the 12 week treatment initiation phase of the model (i.e. the decision tree element). After the assessment of treatment response at 12 weeks, all non-responders were assumed to cease active treatment, and revert to their baseline ESS.

In the TONES 3 IPD, although non-responders did not achieve the model-defined response criteria (≥3 point reduction in ESS), these patients still achieved a small reduction in ESS (reduction <3 points). However, as a result of the centring exercise (Section B.3.3.2) applied to adjust for the placebo effect in each arm, non-responders had a small *increase* in ESS from baseline. In clinical practice it is unlikely that a wake-promoting agent would increase EDS however, the current analysis conservatively incorporated this increased EDS effect as it was reflective of the mIPD from TONES 3. All patients who were responders but subsequently discontinued treatment (in the Markov element) were assumed to discontinue treatment and revert to their baseline ESS (i.e. their pre-solriamfetol level of ESS), as they would be thereafter be receiving standard of care without solriamfetol, and experience the stable level of EDS associated with that standard of care.

B.3.3.5 Clinical data: loss of efficacy on solriamfetol discontinuation

The randomised withdrawal phases of both TONES 5 (Section B.2.6.2.3) and the supporting RCT TONES 4 (Section B.2.6.3) demonstrate that within 2-weeks of solriamfetol discontinuation, patients with OSA experience increase levels of EDS, with mean ESS scores increasing rapidly but not to baseline levels.

Solriamfetol represents the only licensed treatment option for the management of EDS in patients with OSA whose EDS has not been satisfactorily treated by a primary OSA therapy. In the absence of any evidence for a loss of efficacy, and

because solriamfetol is not disease-modifying for the underlying cause of OSA and has a half-life of 7.1 hours, it was assumed that solriamfetol treatment effects diminish rapidly upon solriamfetol discontinuation.

The evidence from TONES 5 and 4 indicates solriamfetol-related effects on EDS diminish over a time course of weeks after discontinuation, and that mean ESS scores increase but may not reach baseline values. For simplicity, the current analysis conservatively assumed an immediate return to baseline ESS scores after solriamfetol discontinuation. As previously noted, all patients receiving standard of care without solriamfetol remained at their baseline ESS for the duration of the analysis, where baseline ESS refers to their ESS on stable standard of care.

B.3.3.6 Adverse events

In TONES 3, AEs with an incidence ≥5% (Table 20) in the placebo, solriamfetol 37.5, 75 and 150 mg arms included headache, nausea, decreased appetite, nasopharyngitis, dry mouth, and anxiety. Most AEs occurred early in the course of treatment (e.g. within the first 1–2 weeks), are self-limiting, and generally resolve quickly (Section B.2.10.5 and Appendix C).

As solriamfetol is the only wake-promoting agent licensed in the UK to manage EDS due to OSA, there is no evidence regarding the management of AEs in clinical practice from similar pharmaceutical agents. However, feedback from KOLs experienced in the use of wake-promoting treatments to manage EDS due to narcolepsy suggests that treatment-related AEs are unlikely to require substantial intervention (144), thus for the purposes of this analysis, the impact of management of AEs was excluded and only the impact of discontinuation due to AEs was considered.

B.3.3.7 Discontinuation of the standard of care treatment for the underlying OSA

Discontinuation of the standard of care treatment (in both arms) was not considered in the current analysis. Consistent with clinical practice where standard of care managed the underlying OSA, the assumptions in the model for TA139, and the evidence from TONES 3 (Section B.2.6.1.8), the current analysis assumed that

patients in both arms continued their standard of care treatment for the underlying OSA for the duration of the model. As a result, patients in the standard of care without solriamfetol arm of the current analysis were neither receiving active treatment for the management of their EDS nor capable of discontinuing standard of care for the underlying OSA.

As previously noted, patients in the placebo arm were incapable of experiencing any increase in ESS scores that would be associated with discontinuing standard of care in clinical practice. Conversely, patients who discontinued solriamfetol treatment could revert to their pre-solriamfetol ESS scores (i.e. their ESS score when receiving standard of care only). This could result in scenarios in which, over time, the standard of care without solriamfetol arm becomes more effective than the standard of care with the addition of solriamfetol arm, due to the inability to discontinue standard of care, and therefore the current analysis reflects a more clinically credible approach.

B.3.3.8 Discontinuation – Due to AEs

Treatment initiation phase: In TONES 3, the incidence of AEs leading to study drug withdrawal and study discontinuation over the course of the 12 week duration were low: 5.2%, 3.2% and 4.3% for solriamfetol 37.5, 75 mg, and 150 mg, respectively, compared with 3.4% for placebo (7.3% for the solriamfetol combined, including the 300 mg dose).

The mIPD assumed that patients who discontinued due to AEs did not achieve any reduction in ESS from baseline, such that they were considered non-responders upon assessment of response at 12 weeks. This approach assumed that the rate of discontinuation due to AEs during the initiation phase (i.e. decision tree component) was implicitly captured in the mIPD and did not need to be considered separately within the current analysis.

Maintenance treatment phase: In TONES 5 discontinuation due to AEs (all doses including the unlicensed 300 mg dose) was observed in 36/417 (8.6%) participants with OSA over the duration of the study, with 56.8% of all AEs occurred within the first 4 weeks of treatment, and the remaining 43.2% occurring after the first 4 weeks

(102). Excluding the unlicensed 300 mg dose, discontinuation due to AEs was observed in [redacted] of patients with OSA over the duration of the study (75 mg, [redacted]%; 150 mg, [redacted]%).

In the current analysis, it was assumed that the annual rate of AE-related discontinuations after titration was 3.7% (i.e. 43.2% of 8.6%), based on the assumption that the rate of discontinuations due to AEs reported at week 4 in TONES 5 (4.9%; 56.8% of 8.6%) was approximate to those that implicitly occurred during the model initiation phase (i.e. the decision tree component) for TONES 3.

The current analysis can therefore be considered a conservative approach, as the observed rates of AEs were dose-dependent for 75–300 mg doses. As the TONES 5 study design utilised a combined solriamfetol arm which included the unlicensed 300 mg dose but did not include the 37.5 mg dose, 8.6% is likely to be an overestimated rate of discontinuations due to AEs and in practice; as described above, excluding the 300 mg dose, discontinuation due to AEs was [redacted]% thus the rates of discontinuation for the licensed doses are expected to be lower. As patients in the standard of care without solriamfetol arm were not receiving active treatment, this was assumed for the solriamfetol arm only.

B.3.3.9 Discontinuation – Loss of response

TONES 3 found no evidence to suggest that treatment with solriamfetol will impact the level of use or compliance to a primary OSA therapy (Section B.2.6.1.8) and therefore it was assumed that the for both treatments in this analysis patients continued their standard of care treatment for the underlying OSA at a stable level throughout the duration of the model, further supporting the use of mIPD. As such, there was no loss of response associated with the standard of care component, and the model only considered loss of response with regards solriamfetol treatment.

In TONES 5, study withdrawal due to loss of response was observed in 15/417 (3.6%) participants with OSA (102). As with discontinuation due to AEs, a proportion of these withdrawals would have occurred during the initiation phase (i.e. the decision tree component). In TONES 3 0.0% of patients discontinued solriamfetol due to loss of efficacy over 12 weeks of treatment (97).

The rate of discontinuations due to loss of response was dose-dependent in TONES 5 – the current analysis used a conservative approach and assumed that 3.6% of patients (3.6% minus 0.0%) would discontinue due to loss of response within the first year.

B.3.3.10 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; as a consequence patients with EDS may have an increased risk of mortality (160). 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 conservatively excluded any excess mortality that may be associated with non-responders to treatment, who are assumed to have a higher level of EDS compared with responders whose EDS is reduced and controlled. The analysis therefore uses general population estimates, as per NICE TA139 (76, 87).

B.3.4 Measurement and valuation of health effects

EQ-5D-5L was collected during the TONES 3 trial to measure the QoL of patients. However, the TONES 3 EQ-5D dataset was not used to directly inform the current cost-effectiveness analysis. The rationale as to why the TONES 3 EQ-5D dataset is not considered an appropriate choice for the model is described below and has been previously considered in the ERG report for NICE TA ID1602 (solriamfetol for treating EDS due to narcolepsy).

A number of subjective and objective measures were collected during TONES 3, including ESS, MWT, FOSQ-10, SF-36v2, PGI-c, CGI-c and WPAI. All of these outcome measures showed improvements in patients with EDS due to OSA treated with solriamfetol, from baseline through to week 12, and in change from baseline versus placebo (either in global or in specific domain scores; see Section B.2.6.1). In contrast, no meaningful trends were observed in domain scores for EQ-5D-5L, utility index scores or VAS scores, but the reason(s) for the lack of effect is/are unclear (Section B.2.6.1.10). The results observed for the EQ-5D are therefore inconsistent

with the other outcome measures assessed in TONES 3, and with previous studies reporting the impact of OSA on patient QoL as measured using QoL tools such as the SF-36 (20, 53, 55, 56, 60, 67).

There are several hypotheses that may explain this anomaly in the TONES 3 EQ-5D data. The EQ-5D does not contain domains that specifically assess two factors known to impact QoL in patients with OSA: EDS and relationships:

- The EQ-5D does not contain a specific domain to examine sleepiness or wakefulness therefore it is possible that in using the EQ-5D, the impact of these factors on the QoL of patients with EDS due to OSA were not adequately captured in TONES 3. Yang 2014 (161) investigated the impact of adding a "sleep" domain to the EQ-5D but found that the sleep domain did not improve the predictive power of EQ-5D for QoL scores. The fact that this domain is being investigated suggests this is an acknowledged limitation with using the EQ-5D to assess QoL in sleep. Although reduced sleep quality can negatively impact short- and long-term outcomes, it is important to note that the absence of an observed benefit to QoL with the added EQ-5D sleep domain indicates that the addition of the proposed sleep domain did not improve the sensitivity of EQ-5D in assessing the QoL impact of sleep, and cannot be considered confirmation that the EQ-5D in its current form is suitable to assess the impact of sleep disorders on QoL. Furthermore, this exploratory domain was for "sleep" and not "EDS" (the outcome of interest in TONES 3), and investigating the addition of an EDS domain to the EQ-5D may be appropriate to identify the impact of EDS on QoL in patients with OSA.
- The EQ-5D does not include a domain to specifically examine the impact of a condition on relationships, however as described in Section B.1.3, relationships are a highly important aspect of HRQoL (45), and qualitative studies show that EDS due to OSA has substantial and long-lasting negative impacts on the patients' interpersonal relationships and family life (18, 40, 44). Therefore, without the inclusion of a relationships or family domain in the EQ-5D, there is potential for a ceiling effect when examining the impact of EDS due to OSA on relationship problems or reduced family interactions, social isolation and their subsequent impact on HRQoL.

Furthermore, a closer examination of the baseline clinical characteristics and QoL status of the patients in TONES 3 indicates that the EQ-5D was incapable of assessing the impact of EDS due to OSA on the QoL of these patients due to a capping effect:

- At baseline, [redacted] of the TONES 3 population had a utility score ≥0.9, suggesting they had limited or no disutility associated with their EDS or OSA at baseline. A comparison of patients with baseline utility ≥0.9 ([redacted]; mean utility [redacted]) with those patients with baseline utility <0.9 ([redacted]; mean utility [redacted]) strongly suggests that the EQ-5D data do not adequately reflect the impact of EDS due to OSA on QoL, nor any solriamfetol-related improvements in QoL. Table 29 presents a comparison of summary baseline and clinical characteristics for patients with baseline EQ-5D utility scores of ≥0.9 compared with <0.9. These data demonstrate that mean ESS scores at baseline were comparable between the groups ([redacted] vs [redacted], respectively) indicating patients in both groups had substantial levels of EDS at baseline. After 12 weeks of treatment, ESS scores for patients with high (≥0.9) or low (<0.9) baseline utility were [redacted] and [redacted] respectively for patients randomised to solriamfetol, compared with [redacted] and [redacted], respectively for patients randomised to placebo. Solriamfetol therefore delivered mean ESS scores [redacted] for patients randomised to solriamfetol; these data demonstrate that regardless of [redacted], the EQ-5D did not detect any improvements in QoL which is inconsistent with the widely accepted burden of ESS and its negative impact on patient QoL, functional status and ability to conduct daily activities (Section B.1.3).

Table 29. TONES 3: summary of patient baseline and clinical outcomes stratified by baseline EQ-5D utility score

	Baseline utility ≥0.9	Baseline utility <0.9
N, %	[redacted]	[redacted]
Compliant* to OSA therapy, n, %	[redacted]	[redacted]
Mean utility score at baseline	[redacted]	[redacted]
Mean ESS score at baseline	[redacted]	[redacted]
Proportion minimally improved on CGI-c at week 12		
CGI-c ≤ 3	[redacted]	[redacted]
Mean utility score at week 12		
Placebo	[redacted]	[redacted]
Solriamfetol	[redacted]	[redacted]
Mean ESS score at week 12		
Placebo	[redacted]	[redacted]
Solriamfetol	[redacted]	[redacted]

Abbreviations: CGI-c, clinical global impression of change; EQ-5D, 5 dimension EuroQol; ESS, Epworth Sleepiness scale.
* See Table 4 for definition of compliance.

- Additionally, [redacted]% of patients overall had mean utility index of 1.0 (placebo, [redacted]%; solriamfetol [redacted]%), yet despite their [redacted], their baseline ESS scores show that these patients suffered from substantial levels of EDS (mean ESS: [redacted] for placebo vs [redacted] for solriamfetol arms), and that these ESS scores were not markedly different for those patients with utility scores [redacted] (mean ESS: [redacted] for placebo vs [redacted] for solriamfetol). These baseline characteristics not only contradict the widely accepted burden and QoL impact on patients with OSA (Section B.1.3) but also demonstrate the inconsistency between the patients' subjective reports of EDS, the clinicians' objective reports of overall illness, and the patients' subjective reports of QoL. This provides evidence that there was limited potential within the TONES 3 trial population to capture any solriamfetol-related improvements on EQ-5D .
- The [redacted] utility scores presented in Table 29 support the argument that the EQ-5D did not suitably capture HRQoL data for the TONES 3 trial population. Given that patients with OSA have multiple comorbidities and the impact of their condition on their QoL is significant, the baseline utility scores (whether or not they are sensitive enough to detect the impact of EDS) are

clearly not reflective of a population with multiple comorbidities, fragmented sleep and a burdensome health status.

Additional evidence that the EQ-5D does not appropriately reflect the QoL burden associated with EDS in the trial population are observed in the overall TONES 3 population. At baseline, 90.5% of patients overall were rated by clinicians (using the CGI-s) as being moderately, markedly, severely or among the most extremely ill. However, despite the severity of their condition, patients in TONES 3 had limited mean disutility on EQ-5D: mean baseline EQ-5D index scores were [redacted] for solriadmfetol 37.5 mg, and [redacted] for both solriamfetol 75 mg and 150 mg, compared with [redacted] for placebo. Furthermore, 78.3% of patients randomised to solriamfetol had clinician-reported improvements[r] in overall condition but despite these objective improvements in the patients' condition, their mean utility scores were minimally changed from baseline to week 12.

Patients with OSA have a chronic condition and are known to adapt their expectations of health and daily life to their condition (23, 44, 54). The above observations from the overall TONES 3 population provide evidence of adaptation in these patients; furthermore, approximately [redacted] of patients reported slight or no problems in the 'usual activities' domain at baseline, despite their substantial levels of EDS (as measured using ESS). The [redacted] utility scores in TONES 3 (Table 29) is also consistent with adaptation, and it indicates that these patients had [redacted], in particular on the usual activities domain. The impact of adaptation on a patient's self-reported QoL is likely to be most apparent in the usual activities domain of EQ-5D however, once a patient with OSA has adapted their daily life to their condition, they may re-define what they consider 'usual activities', such that there is little or no apparent impairment when usual activities are assessed using the EQ-5D. Furthermore, there may be activities an adapted patient wishes to do, that may significantly improve their QoL, but which they are prevented from doing due to their condition. UK KOL

[r] Patients who were at least minimally improved as measured using the CGI-c

Evidence supports the occurrence of adaptation in patients with EDS due to OSA, with KOLs reporting that patients whose EDS is effectively managed using CPAP only realise the impact of their EDS after it is resolved (51); as such, patients whose EDS is not satisfactorily managed by a primary OSA therapy (i.e. those who are eligible for solriamfetol) may remain unaware of the impact of their EDS on QoL and therefore continue to tolerate their reduced QoL, until their symptom is effectively managed. The EQ-5D does not address the disutility associated with a scenario of adaptation and although adaptation is a possibility for all chronic conditions, studies and UK KOL Evidence show that patients with EDS due to OSA underestimate the impact of their EDS on their every day life (51, 54).

This discrepancy between patient characteristics and subjective QoL is also evident within data from the EU5 National Health and Wellness Survey (NHWS) comprising of patients with OSA or narcolepsy (Appendix M). Approximately two-thirds of patients (n=1,557) in the NHWS had ESS scores in the normal range (ESS ≤10) and therefore a higher proportion of patients reporting a utility score of 1 may be expected. However, in contrast to the disutility observed in TONES 3 ([redacted]) only [redacted] of the NHWS population had a baseline utility score of 1 further supporting the theory that the TONES 3 EQ-5D dataset would be inappropriate to use in the current analysis. The NHWS analysis also demonstrated that the impact of EDS on QoL was greater for patients with ESS scores ≥12 compared with those with ESS scores ≤11, showing the impact on QoL increased with higher levels of EDS.

Although not directly applicable to the current submission, additional information from the TONES 2 population of patients with EDS due to narcolepsy support the decision to exclude the TONES 3 EQ-5D dataset from the current analysis. For TONES 2, interaction tests carried out on EQ-5D-5L data for each of the five domains in the US vs non-US patients showed a difference in the slope between the two populations. There were also differences between the populations across these geographies, which may have affected the sensitivity of EQ-5D to detect the impact of EDS on QoL; the TONES 3 population comprised patients from the US, Canada and Europe (France, Germany, Netherlands), therefore geographical variations in usual activities may have affected the impact of EDS on QoL. Similar assessment of

the European patient dataset from the TONES 3 trial was considered, however small patient numbers (Table 19) restricted any meaningful analyses.

B.3.4.1 Health-related quality-of-life studies

In the absence of appropriate trial-based EQ-5D data for incorporation in the cost-effectiveness analysis (Section B.3.2), an SLR was conducted to identify studies reporting on the HRQoL of patients with OSA. Full details of the methodology and results of the studies identified are presented in Appendix H.

In total, 36 records for 34 unique studies were identified which reported HSUVs for patients with OSA, eight of which were conducted from a UK perspective (151, 154, 162-167) and five of which fully met the requirements of the NICE reference case (151, 152, 154, 162, 166). The HRQoL SLR also identified a single relevant HTA (NICE TA139 for CPAP in the treatment of OSAHS (76, 87)) which was interrogated for relevant information on utility values and related methodological details.

The majority of the 34 unique HRQoL studies identified considered QoL in patients with OSA pre- vs. post-primary OSA therapy interventions (primarily CPAP), inferring a QoL impact associated with the treatments considered. This is consistent with the current modelling approach, in that QoL remains stable once patients are established on stable level of use of their primary OSA therapy. EDS was only an explicit consideration in one study (Hessmann 2017 (168)) which did not meet the reference case for consideration, and only two publications undertook regression analyses to link ESS to utilities (163, 167), however it is likely that the QoL impact observed was partly linked to treatment-related effects on EDS. The two studies using regression analyses utilised the same analysis presented in NICE TA139, and the corresponding coefficients are presented in Table 30. As these studies were based on TA139, and no other evidence in meeting the NICE reference case was identified, only HRQoL data from TA139 was considered in the current analysis.

Table 30. Coefficients from utility analysis from NICE TA139 (76)

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.3.4.2 Mapping

In the absence of suitable trial-based EQ-5D utilities from TONES 3 (as outlined in Section B.3.4), and based on the studies identified by the SLR (Section B.3.4.1), an alternative approach to modelling utilities was undertaken to align this submission with the ESS to EQ-5D mapping exercise undertaken in TA139 (McDaid approach (76)). Following similar methodology, two options were considered for inclusion in the current cost-effectiveness analysis, as described below:

- McDaid algorithm (Table 30)
- De novo analysis of NHWS data (Appendix M)

B.3.4.2.1 The McDaid algorithm

The McDaid algorithm was developed by the Assessment Group for TA139 to inform NICE TA139 in assessing CPAP for OSAHS (76). The EQ-5D-ESS algorithm was developed using a sample of 94 patients with OSA, and uses a linear regression model – a test was performed to check for evidence of a change of slope, however there was no evidence to support this effect, likely down to the small sample size.

B.3.4.2.2 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.

For the current analysis, 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 detail in Appendix M). This analysis was considered to have good processes for data analysis and model fitting by the ERG for NICE TA ID1602 (solriamfetol for the management of EDS due to narcolepsy). Across the full population (OSA and narcolepsy), the analysis shows a similar, but shallower slope compared with the McDaid analysis, suggesting that there is more impact on a patient if their ESS is >11 compared with ≤11. 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. Figure 19 illustrates the relative differences between McDaid and NHWS, and shows that the utility slope for ESS scores >11 (i.e. presence of EDS) was steeper than the slope for ESS scores ≤11. Given the proximity of the break point of 11.29 on the ESS scores in this analysis, to the widely accepted threshold for 'normal' EDS (ESS=10; see Table 6), this is consistent with the expectation that once patients achieve normal or near normal ESS scores (i.e. no or very mild EDS), any further improvement towards the lower range of normal ESS scores does not notably improve their QoL. Despite this, it would be inappropriate to suggest based on this finding that patients who achieve a score of <11 could be considered a responder as UK KOL Evidence indicates the individual patient impact of EDS is highly variable (51); instead this effect suggests that a ≥3 point reduction in ESS scores for patients with a higher baseline ESS could have a more substantial impact on their function, dailiy life and QoL, compared with patients who achieve a ≥3 point reduction from lower baseline ESS scores.

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

Abbreviations: EQ-5D, 5-dimension 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 3, nor any data available from the literature to populate this algorithm in a manner reflective of the UK population. As such, the sample average from the NHWS dataset has been used (as described in Appendix M).

There are some factors that may explain the slightly shallower overall slope observed in the NHWS analysis compared with the McDaid analysis. First, the de novo analysis of the NHWS dataset may have been influenced by confounding variables that were not captured, and furthermore, income and exercise may have had an effect:

- **Income** – patients on an income of £/€20,000–£/€40,000 [redacted] compared with those patients earning <£/€20,000, but there was [redacted] at incomes greater than £/€40,000. This suggests that the greatest improvement in QoL is observed when patients transition from [redacted] income, towards [redacted] national income. Given the impact that EDS has on work productivity and output, it is possible that over time, improving a patient's EDS could contribute towards improved capacity to work, which subsequently can improve their income and consequently the patient's QoL.
- **Exercise** – A patient capable of a moderate amount of exercise has [redacted] in utility compared with a patient who is unable to partake in moderate exercise. It is likely that a patient who feels less sleepy due to improvements in their EDS might feel more able to do regular exercise which could further improve their quality of life (169). This is particularly important in patients with OSA, who may have multiple comorbidities including obesity, diabetes or cardiovascular disease, and for whom increased ability to exercise could contribute to long-term gains in QoL and/or length of life.

Although the EQ-5D was inadequate for capturing QoL improvements in TONES 3, it appears that this was related to the [redacted] of the trial patients (who had [redacted]). Based on the above and the positive opinions on this dataset by the ERG for NICE TA ID1602, who agreed in the use of the NHWS mapping algorithm in the base case for that submission, the NHWS was considered to be the most robust of the two alternative datasets examined, and was thus chosen as the base case source of utility data for this submission, with the McDaid algorithm assessed in a scenario analyses.

B.3.4.3 Adverse reactions

As described in Section B.3.3.6, the incidence of AEs has not been considered in the base case analysis and thus utility decrements resulting from AEs are not modelled.

B.3.4.4 Health-related quality of life data used in the cost-effectiveness analysis

B.3.4.4.1 HRQoL: National Health and Wellness Survey

The HRQoL of the cohort over the time horizon of the model was considered by assigning a utility value to the treatment-adjusted ESS using the NHWS mapping algorithm outlined in Section B.3.4.2.

Patients entered the model with a baseline ESS score (derived from the TONES 3 mIPD), and this was used to calculate an associated utility value using the NHWS mapping algorithm (Section B.3.4.2). Patients were assessed to be responders or non-responders and were attributed a reduction in ESS from baseline, which was then used to estimate the treatment-related ESS score. This treatment-adjusted ESS score was then used to estimate a treatment-related utility using the NHWS mapping algorithm. In the base case it was assumed that for all treatments and for responders and non-responders, the reduction in ESS occurred within 1 week of treatment initiation and persisted until response was clinically assessed at week 12.

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

Table 31. Mean ESS when receiving treatment in responders and non-responders and the associated mean utilities

Product, daily dose	Mean ESS in responders	Mean utility of responders up to week 12	Mean ESS in non-responders	Mean utility in non-responders up to week 12
Standard of care with solriamfetol 37.5 mg	[redacted]	[redacted]	[redacted]	[redacted]
Standard of care with solriamfetol 75 mg	[redacted]	[redacted]	[redacted]	[redacted]
Standard of care with solriamfetol 150 mg	[redacted]	[redacted]	[redacted]	[redacted]
Standard of care without solriamfetol	Not applicable*		[redacted]	[redacted]

Abbreviations: ESS, Epworth Sleepiness Scale.
* Due to the centering exercise conducted to adjust for the placebo effect (Section B.3.3.2), there were no responders in the standard of care arm by default.

Table 31 shows the mean ESS in responders and non-responders for each comparator treatment, derived from the mIPD from TONES 3 (Section B.3.3.1). These values were then applied to the NHWS mapping algorithm to estimate the corresponding utility value. Patients who had not achieved a 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 outlined previously, the associated utility values were re-estimated in each cycle to account for the age covariate in the NHWS mapping. An alternative scenario using the McDaid 2007 mapping algorithm (Section B.3.8.4) was also considered.

B.3.4.4.2 HRQoL: Time trade off analysis

The NICE reference case specifies the inclusion of wider HRQoL impacts can be captured where appropriate (149), and given the impact of EDS on the patient's partner (Section B.1.3), it was therefore considered appropriate to include the utility of the partners in the current analysis. However, no such partner utility data have been published to date which could be used to inform an economic model, representing a limitation in capturing the wider impacts of EDS due to OSA. A time trade off (TTO) study is a viable method of capturing the effects of a disease on patients, and their partners and carers, therefore a TTO study was conducted using members of the UK general public (England and Scotland) to elicit utility values for

use in the current analysis for both the patients with EDS due to OSA and their partners.

The TTO assessed the health states and associated utility values for increasing levels of EDS severity over a 10 year horizon; [redacted]. Health states were developed around the EQ-5D construct, reviewed by an expert sleep physician and posted on an online bulletin where a combination of patients with EDS, partners of patients with EDS, and clinical experts in the field were invited to comment and answer the questions posed. The health states were revised in response to the feedback from the bulletin board before being further validated by the same sleep physician that first reviewed them, a final version being produced and used in the TTO study.

Participants evaluated eight health states, that comprised two sections: (i) a base health state representing a typical patient using CPAP, (ii) a specific health state reflecting the impact of EDS in the given health state for patients and partners. The base health state description was included across all patient and partner health states to prevent CPAP being included in the evaluation exercise but retaining it within the health states. The accompanying health state descriptions were developed to enable the participants to imagine themselves as the patient or partner of a patient with EDS across the four health states reflecting increasing levels of EDS: Normal (ESS ≤10), ESS 11–14, ESS 15–18, and ESS ≥19. A total of 104 participants were included in the final analysis and the sample was broadly generalisable to the UK population (well-matched across age, gender, and country location). The mean utility values derived from the TTO exercises are shown in Table 32 for each of the patient and partner health states.

Table 32. Average TTO utility values for patient and partner health states

TTO Utility Values*		Mean	SD (±)	Lower CI (2.5%)	Upper CI (97.5%)	ANOVA†
Patient Health States	1. ESS ≤10	0.9258	0.1088	0.9044	0.9472	[redacted]
	2. ESS 11–14	0.7938	0.1676	0.7608	0.8269	
	3. ESS 15–18	0.6144	0.2190	0.5716	0.6572	
	4. ESS ≥19	0.5457	0.2416	0.4990	0.5923	
Partner Health States	5. ESS ≤10	0.9545	0.0800	0.9389	0.9700	
	6. ESS 11–14	0.8817	0.1335	0.8564	0.9070	
	7. ESS 15–18	0.7514	0.2254	0.7067	0.7962	
	8. ESS ≥19	0.6700	0.2624	0.6195	0.7206	

Abbreviations: ANOVA, analysis of variance; CI, Confidence Interval, EDS, excessive daytime sleepiness; SD, standard deviation; TTO, time trade-off
* All values rounded to four decimal places.
† Tukey's HSD post-hoc analyses are not presented.
‡ Significance level of 0.05

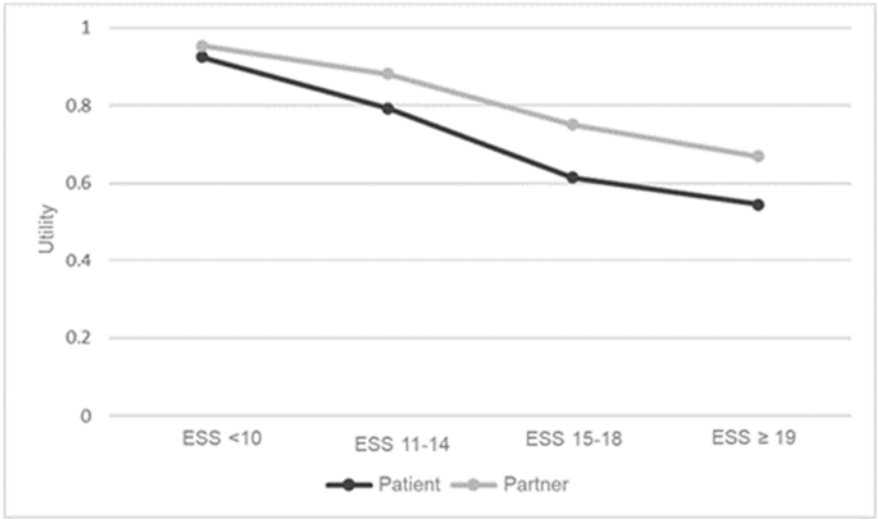
The mean (SD) values ranged from 0.55 (0.24) to 0.92 (0.11) and 0.67 (0.26) to 0.95 (0.08) for the patient and partner health states, respectively. These utility values are reflective of increasing levels of EDS in patients using CPAP effectively. The lower range reflects a patient [redacted] The higher range reflects a patient using CPAP who has persistent EDS (ESS ≥19) and is unable to stay awake, has frequent headaches, is unable to finish meals/chores/conversations without falling asleep, cannot work and has anxiety about finances, cannot be physically intimate with their partner, depends on their partner for care, experiences panic attacks, breakdowns in relationships and friendships, and suffers from depression.

Similarly for the partner utility values, the utility values reflect the impact on the partner of increasing levels of EDS in patients using CPAP effectively. The lower range represents the partner of a patient [redacted] By contrast, the higher range reflects the partners of patients [redacted]

[redacted]

The situations experienced by the patients and their partners are co-dependent on the impact of the EDS on the patient, whereby the patient's inability to partake in family life decreased with higher levels of EDS. The results observed a correlation between patient and partner utility values, such that patient and partner utility increased/decreased concurrently. Mean utility values decreased with increasing EDS, and were typically lower for patient health states compared with corresponding partner health states (Figure 20).

Figure 20. Mean TTO utility values for patients and partners by health state



*

Abbreviations: ESS, Epworth Sleepiness Scale; TTO, time trade off.

Across the patient health states, the differences between the mean utility values observed for each health state

[redacted] however [redacted] demonstrating that greater levels of patient EDS were associated with decreasing HRQoL scores for the partners.

Comparison of the EQ-5D data from the EU5 NHWS Data (Appendix M), the TTO data (Appendix N) and the McDaid-derived data using the NHWS survey health state categorisation by ESS score, showed that

t

(Figure 21).

Figure 21. Mean utility values NHWS, McDaid and TTO, for patients by health state using the NHWS ESS categorisation

Abbreviations: EQ-5D-3L, 5 dimension EuroQoL, 3 level; EQ-5D-5L, 5 dimension EuroQoL, 5 level; ESS, Epworth Sleepiness Scale; NHWS, National Health and Wellness Survey; OSA, Obstructive Sleep Apnoea; TTO, Time Trade-Off.

This could be attributed to the EQ-5D being a generic preference measure that was not developed to capture EDS and relationship aspects (Section B.3.4)

. Conversely, it is possible that

. It is not unusual for a directly valued study to observe a larger gradient than a generic measure (170), and

Further, in the TTO study, particular attention was given to the health states development and validation being robust and

representative of patient experience, (with these based on the EQ -5D domains providing the contextual framework for the descriptors used, and with both in-depth clinical expert and patient involvement in their construction). Hence, the health state descriptions were developed to be representative of the patient experience of the impact of increasing levels of EDS on HRQoL, so the decline in utility observed with increasing EDS can be considered plausible relationship.

Consistent with the patient and partner burden outlined in Section B.1.3, the results of the TTO demonstrate the detrimental impact of EDS due to OSA on the HRQoL of both the patients and partners of patients with EDS, based on a study of public preferences in the UK. Patient and partner utility values followed an expected pattern of decreasing utility values with increasing EDS levels.

Beta regression analyses were conducted to obtain estimates for patient/ partner utility values for each individual ESS score (Figure 22). To perform the regression analysis, the observed TTO utility values were applied to the middle of the corresponding ESS range:

- No EDS (0-10); Mid Value = 5, Patient Utility Value = 0.9258, Partner Utility Value = 0.9545
- Mild EDS (11-14); Mid Value = 12.5, Patient Utility Value = 0.7938, Partner Utility Value = 0.8817
- Moderate EDS (15-18); Mid Value = 16.5, Patient Utility Value = 0.6144, Partner Utility Value = 0.7514
- Severe EDS (19-24); Mid Value = 21.5, Patient Utility Value = 0.5457, Partner Utility Value = 0.6700

Figure 22. Beta Regression Analysis of Patient and Partner ESS utility values

Abbreviations: ESS, Epworth sleepiness scale

The beta regressions were performed with these inputs to generate a function in the form: [redacted] to predict the utility value for a given ESS score between 0 and 24 and to align with the model structure. Here,

[redacted]. Resulting in the following functions:

Patient utility Beta Regression Function:

[redacted]

Partner utility Beta Regression Function:

[redacted]

B.3.4.4.3 Partner utilities

The NICE reference case states that the perspective on outcomes should be for all direct health effects, whether for patients or other people. There is a substantial burden of EDS due to OSA experienced by the partner of patients, which affects their relationship, family life and daily function (Section B.1.3). As such, a scenario analysis was conducted where the impact of EDS due to OSA on the partners of patients was considered, using assumptions derived from the TTO utility analysis

(Appendix N).

[redacted] The trend line derives from the equation:

[redacted].

Figure 23. Correlation between patient and partner utilities in the TTO study

Abbreviations: TTO, time trade off.

[redacted]

According to the Office for National Statistics (ONS), approximately 66% of those aged over 50 are living as a couple (171). Therefore, for the purposes of the scenario analysis it was assumed that the impact to partners would only be attributable to 66% of patients.

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

B.3.5.1 Intervention and comparators' costs and resource use

B.3.5.1.1 Standard of care for the underlying OSA

Both treatment arms considered in the current analysis contained a standard of care component to manage the underlying cause of OSA, thus the costs and resource use associated with standard of care were not considered, and only the cost of solriamfetol as an add-on treatment to standard of care was assessed.

B.3.5.1.2 Solriamfetol

Solriamfetol is available as 75 mg and 150 mg film-coated tablets – administration of the 37.5 mg dose can be achieved by halving a 75 mg tablet using the score line. The recommended starting dose for patients with OSA is 37.5 mg once daily, upon awakening; depending on clinical response, the dose may 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. The rationale for a 3 day interval as a minimum duration between dose titration relates to the time taken for solriamfetol to reach plasma steady state and is the standard that was used in the TONES clinical trial programme, however it is expected that in clinical practice titration will occur over significantly longer intervals. Treatment with solriamfetol should be initiated by a healthcare professional experienced in the treatment of OSA or narcolepsy (Appendix C).

There is no information available to inform the intervals between titration from the starting dose of 37.5 mg to higher doses of solriamfetol. In TONES 3 the doses were selected by randomisation and in TONES 4 and 5, solriamfetol titration was started at 75 mg and forced to the maximum tolerated dose, such that some patients may have up-titrated based on good tolerability, but in clinical practice may not have required the higher dose from an efficacy perspective. The interval between titration in clinical practice is expected to be longer than the 3 days described in the SmPC, as clinicians will likely titrate slowly to assess response and tolerability. For simplicity, to avoid any uncertainty around the costs associated with receiving lower

doses at variable intervals before titration (as expected in practice), this analysis conservatively assumed that throughout the first 12 weeks of the model, patients received the cost of the highest dose that they titrated to, thus attributing a penalty to solriamfetol as these costs are higher than would be expected in practice. The cost of solriamfetol equated to:

- A 12 week cost of £293.53, £559.81 and £800.42 for the 37.5, 75 and 150 mg daily doses, respectively.
- For patients that continued treatment beyond 12 weeks, a weekly cost of £22.19, £44.38, and £62.16 was assumed for the 37.5, 75 and 150 mg doses, respectively.

The dosing in TONES 3 was determined by randomisation, whereas in TONES 5 investigators were protocol-driven to titrate from a starting dose of 75 mg to the highest tolerated dose (maximum 300 mg, however this dose is not licensed). Therefore, 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 also presented a combined analysis using a 40/40/20 split of the three doses. Data from the US suggest a [redacted] dose split for each of 37.5, 75, and 150 mg doses, respectively, but it is anticipated that UK prescribers will be more conservative than those of the US, leading to a 40/40/20 dose split. The dose split is varied in the sensitivity analyses.

Based on the Sleep Services Analysis and UK KOL Evidence, after a patient's initial diagnosis of OSA by a consultant, the treatment and management of OSA (i.e. standard of care) is typically physiologist- or technician-led, however clinicians are likely to titrate solriamfetol in the clinic (51, 90). The current analysis assumed that patients with EDS due to OSA would be initiated onto solriamfetol 37.5 mg during an initial appointment with a consultant. However, this visit was assumed to occur in both arms – because in clinical practice, a patient who is receiving standard of care without solriamfetol (i.e. primary OSA therapy for the underlying condition) would present with persistent EDS but be advised by a consultant that there was no intervention available to manage their EDS. As such, it was assumed that the

introduction of solriamfetol would not require an additional consultation for treatment initiation.

During this initial consultation wherein a patient presents with EDS due to OSA, they would be prescribed the 37.5 mg dose of solriamfetol and be advised to titrate from 37.5 mg to 75 mg if their response was insufficient (based on the patient's personal impression of improvement). All patients would then have a consultant-led contact 12 weeks after treatment initiation (based on the primary endpoint in TONES 3), during which the patient's treatment response would be assessed, and their HR/BP would be monitored (as per the SmPC). Based on the IPD from TONES 3 (Table 28),

[redacted] It was therefore assumed that only patients who do not achieve optimal response to the lower doses of solriamfetol would be expected to titrate to a higher dose.

At their 12 week visit, if patients who have self-titrated to solriamfetol 75 mg report no response to treatment, further titration to 150 mg would be appropriate and the patient would be prescribed the 150 mg formulation. At a subsequent visit (at an interval determined by individual clinic capacity), those patients who titrated to 150 mg would receive an additional consultation to assess their treatment response to the higher dose.

In summary, all patients continuing the solriamfetol 37.5 or 75 mg dose beyond 12 weeks would require one incremental consultation, whilst those who titrate to the 150 mg dose would require two incremental consultations. For the purposes of the current analysis it was assumed that each consultant contact would be 15 minutes with a hospital-based medical consultant. Curtis and Burns 2019 provides an associated cost of £109 per hour which equates to £27.25 per face-to-face contact (156).

B.3.5.2 Health-state unit costs and resource use

As described in the Sleep Services Analysis and supported by UK KOL Evidence, there is no consensus on the interval between routine follow-ups, which varies

according to the individual centre's capacity (51, 90). Further, patients with OSA are receiving standard of care for their underlying OSA, and are likely to have frequent routine follow-ups for comorbidities, including obesity, hypertension, diabetes, hyperlipidaemia, and high BMI. As such, following the patient's initial assessment of response at 12 weeks (or subsequent appointment for the small proportion of patients expected to titrate to the 150 mg dose), the patient's response and tolerability to solriamfetol, in addition to the BP and HR monitoring, could be assessed during routine follow-ups for their underlying OSA or comorbid conditions. For example, NICE Guidance 136 recommends annual blood pressure monitoring for patients with hypertension, thus this would occur as part of routine care for these patients (172). This is supported by UK KOL Evidence that the introduction of solriamfetol would have minimal impact to routine care and is unlikely to increase clinic workload as these patients are already repeat attendees at clinics (51).

As previously described, all AEs in TONES 3 were transient and the majority were mild/moderate in severity, therefore in the base case analysis, treatment-related AEs that did not lead to discontinuation were not considered. 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 (156). For simplicity, no disutilities were considered as the minimal duration and relative impact on QoL would cause only a nominal impact on overall QALYs.

B.3.5.3 Miscellaneous unit costs and resource use

Not applicable. As described above, patients with OSA typically have multiple comorbidities so these patients were assumed to receive regular monitoring and follow-up visits for their comorbidities and their underlying condition, thus this analysis assumed that there would be no incremental resource use associated with solriamfetol treatment.

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

B.3.6.1 Summary of base-case analysis inputs

Table 33: Summary of variables applied in the economic model

Variable	Value	Measurement of uncertainty and distribution: CI (distribution)	Source
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	[redacted]	[redacted]	Table 25
Proportion of cohort that are female	[redacted]	[redacted]	
Solriamfetol - 75 mg: Pack size	28.0	28.0 - 28.0 (Not varied)	Table 2
Solriamfetol - 150 mg: Pack size	28.0	28.0 - 28.0 (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)	
ESS => EQ-5D: McDaid - Constant	0.893	0.836 - 0.949 (Normal)	B.3.1
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)	
Discontinuation - LoE (Year 1): solriamfetol 150 mg	3.6%	1.81% - 5.38% (Beta)	B.3.3.9
Discontinuation - LoE (Year 1): solriamfetol 75 mg	3.6%	1.81% - 5.38% (Beta)	
Discontinuation - LoE (Year 1): solriamfetol 37.5 mg	3.6%	1.81%% - 5.38% (Beta)	
Discontinuation - TEAEs (Year 1): solriamfetol 150 mg	3.7%	2.56% - 4.89% (Beta)	B.3.3.7
Discontinuation - TEAEs (Year 1): solriamfetol 75 mg	3.7%	2.56% - 4.89% (Beta)	
Discontinuation - TEAEs (Year 1): solriamfetol 37.5 mg	3.7%	2.56% - 4.89% (Beta)	
Cost of discontinuation - TEAEs	£37	£30 - £44 (Gamma)	B.3.3.7
NHWS mapping - Constant coefficient	[redacted]	[redacted]	B.3.4.2
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]	

Variable	Value	Measurement of uncertainty and distribution: CI (distribution)	Source
NHWS mapping - CCIQuan coefficient	[redacted]	[redacted]	
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]	
Proportion of patients receiving solriamfetol 37.5 mg	40%	20% - 60% (Dirichlet)	B.3.5.1
Proportion of patients receiving solriamfetol 75 mg	40%	20% - 60% (Dirichlet)	
Proportion of patients receiving solriamfetol 150 mg	20%	0% - 40% (Dirichlet)	

Abbreviations: BMI, body mass index; CCIQuan, Charlson Comorbidity Index (calculate using the Quan 2011 scoring algorithm (173)); 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 using in the economic model

Table 34. Assumptions and justifications used in the economic model

Assumption	Brief justification	Source
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 (144), however the literature supports a reduction of between 2-4 points in ESS as being a clinically meaningful change (110-112).	B.3.2
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.3.2
This analysis did not consider the impact of EDS on RTAs	Although EDS is associated with an increased risk of RTA, OSA 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 3 IPD for those each treatment considered – This data was centred to account for the placebo effect	The use of IPD allows flexibility in consideration of baseline ESS, the definition of response and the associated impact of treatment on ESS. The data has been centred to adjust for the potential placebo effect and to remove the necessity to discontinue patients on standard of care, who in clinical practice, will not have changed from the original starting position.	B.3.2
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 their baseline ESS when they stopped receiving an active treatment.	B.3.3.5
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 minor, 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.3.3.6

Assumption	Brief justification	Source
Utility inputs		
The NHWS mapping algorithm is used to estimated utilities in responders and non-responders	The NHWS represents a large non-US dataset of patients with OSA or narcolepsy allowing for the most robust elicitation of EQ-5D based utility values linked to ESS, the primary measure of efficacy in the analysis.	B.3.4.2.2
MRU and cost inputs		
Costs associated with standard of care without solriamfetol have been excluded	Solriamfetol will be given in addition to standard of care (the comparator being standard of care without solriamfetol). There is no reason to anticipate that the introduction of solriamfetol will impact the delivery of standard of care and as such, there will be no incremental cost in standard of care (i.e. established clinical management without solriamfetol) for those patients receiving solriamfetol compared with those not receiving solriamfetol. For simplicity, the cost of standard of care has therefore been excluded from the analysis, as these costs are considered equal for both arms.	Table 2 B.3.5.1
There were no health state related costs considered within the analysis	This analysis focuses on the management of EDS in patients with OSA and not the underlying OSA itself. Patients are routinely reviewed and monitored by HCPs and based on UK KOL Evidence, the presence of EDS is unlikely to impact the frequency of routine follow-ups. It could be assumed that patients receiving standard of care without solriamfetol who experience persistent 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

The base case clinical and economic outcomes, generated from the mIPD data, are presented in Table 35. Over the life-time horizon, the ICER of standard of care with the addition of solriamfetol versus standard of care without solriamfetol was £34,106 per QALY. The base case model included half-cycle correction, excluding this had minimal impact on the ICER. Clinical outcomes from the model and disaggregated results of the base-case cost-effectiveness analysis are provided in Appendix J.

Table 35: Base-case results – weighted ICER

Technologies	Total costs (£)	Total QALYs	Total LYG	Incremental costs (£)	Incremental QALYs	ICER versus baseline (£/QALY)
Standard of care without solriamfetol	£0	11.054	29.280			
Standard of care with the addition of solriamfetol (40/40/20 37.5, 75, 150 mg)	£7,402	11.271	29.280	£7,402	0.217	£34,106

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

Due to the relatively small sample size for each solriamfetol dose in TONES 3, a scenario analysis utilising bootstrapping methods, as detailed in Section B.3.3.3, was conducted and the results are presented in Table 36. The results are highly congruent with the base case results.

Table 36: Base-case results using the bootstrapping method – weighted ICER

Technologies	Total costs (£)	Total QALYs	Total LYG	Incremental costs (£)	Incremental QALYs	ICER versus baseline (£/QALY)
Standard of care without solriamfetol	£0 (£0 - £0)	11.135 (11.126 - 11.144)	29.641 (29.602 - 29.679)			
Standard of care with the addition of solriamfetol (40/40/20 37.5, 75, 150 mg)	£7,443 (£7,404 - £7,482)	11.354 (11.345 - 11.363)	29.641 (29.602 - 29.679)	£7,443	0.219	£33,967

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

B.3.8 Sensitivity analyses

B.3.8.1 Probabilistic sensitivity analysis

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 current model used the bootstrapping methods previously described (Section B.3.3.1) to generate a cohort of patients from the IPD for each subsequent draw of input parameters. According to Gray 2010 (159) and Efron 1994 (who introduced this methodology) (174), bootstrapped samples should be equal in size to the original dataset. Thus, each PSA iteration combined the results from one non-parametric bootstrap sample of equal size to each respective arm of the original TONES 3 data (n=54), with one set of random draws from the distributions for other model parameters. By using the IPD to sample patients, the associated uncertainty with regards patient age and the proportion of female patients was automatically captured and was therefore not included as a specific parameter in the PSA.

PSA 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 Beta distribution was assigned to probabilities, proportions, and data 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 (SD) associated with each parameter. If the SD was not available from the reporting study, it was calculated based on the following assumption:

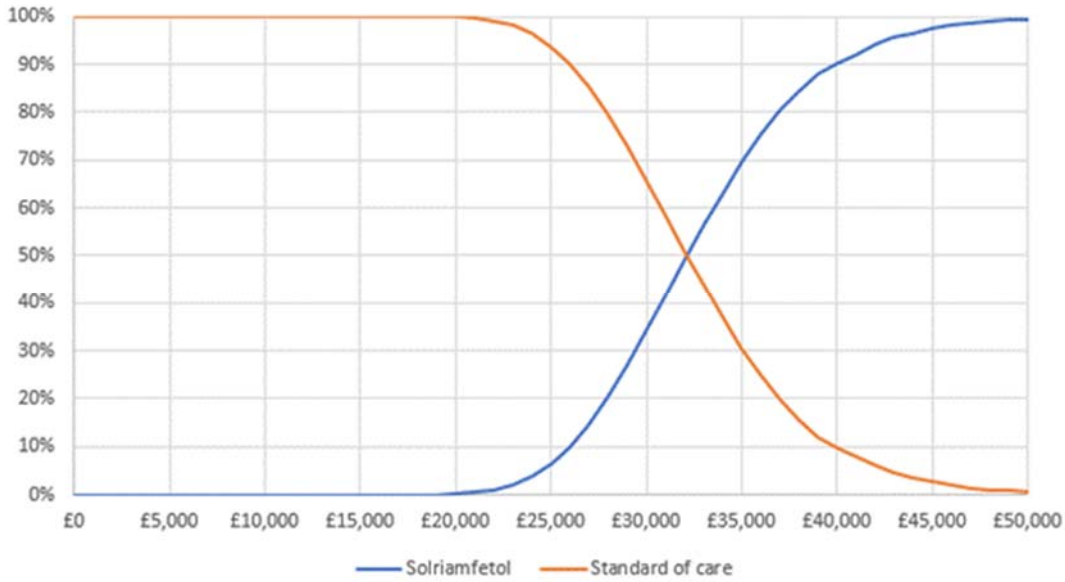
*= (Upper range – lower range)/(2*NORMSINV(0.975))*

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 (159). A total of 5,000 Monte Carlo simulations were recorded, this number was identified as a quantity that resulted in a stable cumulative mean ICER such that additional simulations would not materially impact the conclusions of the analysis. 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 would be the most cost-effective treatment at a threshold of £20,000 per QALY was 0%, and at a threshold of £30,000 per QALY, this increased to 34% (Figure 24). Across 5,000 PSA simulations, solriamfetol was associated with a mean cost of £6,770 (95% CI: £6,734, £6,807) and mean total QALYs of 11.460 (95% CI: 11.450, 11.470) (Table 37). These results are highly congruent with the deterministic results. Overall, the results remain consistent with the base case analysis.

Figure 24. Cost-effectiveness acceptability curve



Abbreviations: SoC, standard of care.

Table 37. Probabilistic sensitivity analysis results

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER incremental (£/QALY)
Standard of care without solriamfetol	£0 (£0 - £0)	11.249 (11.239 - 11.259)			
Standard of care with the addition of solriamfetol (40/40/20 37.5, 75, 150 mg)	£6,770 (£6,734 - £6,807)	11.428 (11.418 - 11.438)	£6,770	0.211	£32,092

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

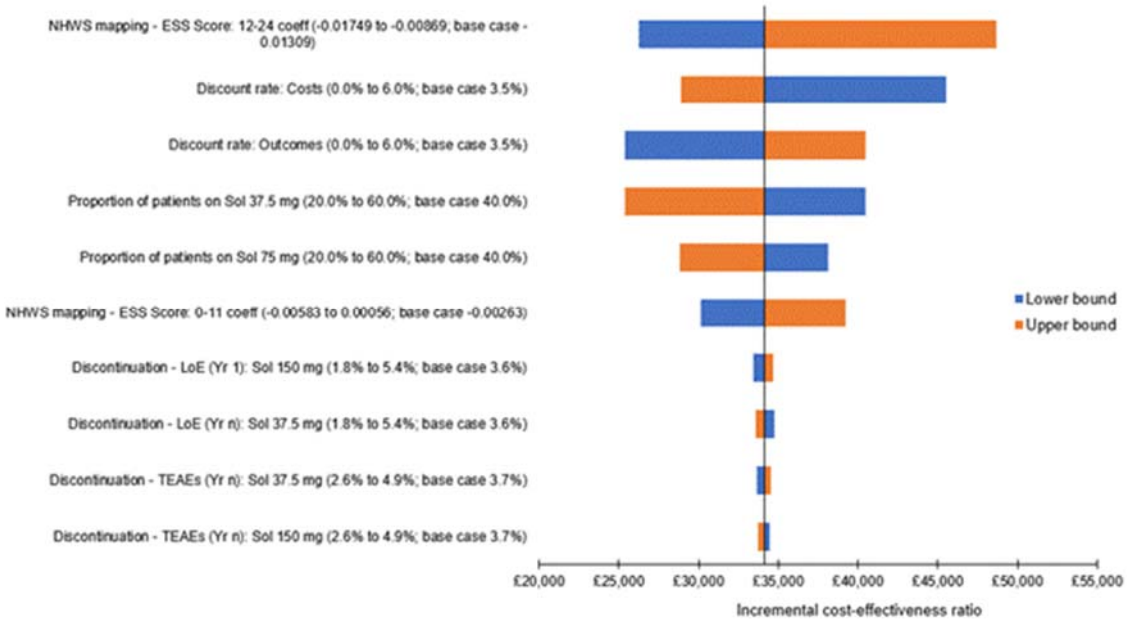
B.3.8.2 Deterministic sensitivity analysis

Parameter uncertainty was tested by univariate sensitivity analysis, in which all model variables were systematically and independently varied over a plausible range determined using either the 95% CI, or +/- 20% where no estimates of precision were available. To avoid the unnecessary introduction of uncertainty, the univariate analysis was based on the TONES 3 mIPD dataset; the bootstrapped results were congruent with those produced using the raw IPD, and the analysis based on the mIPD 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 25 presents the results of the univariate sensitivity analysis standard of care with the addition of solriamfetol versus standard of care without solriamfetol in the form of a tornado diagram. Note that all parameters were varied (Table 33) but the tornado diagrams show the 10 parameters with the greatest impact. These results are also presented in Table 38. The most influential parameters included:

- The discount rates associated with costs and outcomes
- The proportion of patients on solriamfetol 37.5 mg and 75 mg
- Two coefficients of the NHWS mapping related to ESS score, and
- Discontinuation rates associated with solriamfetol

Figure 25. Results of univariate analysis: standard of care with the addition of solriamfetol versus standard of care without solriamfetol



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

Table 38. Results of univariate analysis: standard of care with the addition of solriamfetol versus standard of care without solriamfetol

Variable (lower bound to upper bound; base case value)	ICER with lower bound	ICER with upper bound
NHWS mapping - ESS Score: 12-24 coeff ([redacted] to [redacted]; base case -0.01309)	£26,239	£48,707
Discount rate: Costs (0.0% to 6.0%; base case 3.5%)	£45,558	£28,881
Discount rate: Outcomes (0.0% to 6.0%; base case 3.5%)	£25,361	£40,472
Proportion of patients on Sol 37.5 mg (20.0% to 60.0%; base case 40.0%)	£40,482	£25,417
Proportion of patients on Sol 75 mg (20.0% to 60.0%; base case 40.0%)	£38,106	£28,836
NHWS mapping - ESS Score: 0-11 coeff ([redacted] to [redacted]; base case -0.00263)	£30,167	£39,227
Discontinuation - LoE (Yr 1): Sol 150 mg (1.8% to 5.4%; base case 3.6%)	£33,453	£34,654
Discontinuation - LoE (Yr n): Sol 37.5 mg (1.8% to 5.4%; base case 3.6%)	£34,726	£33,575
Discontinuation - TEAEs (Yr n): Sol 37.5 mg (2.6% to 4.9%; base case 3.7%)	£33,638	£34,528
Discontinuation - TEAEs (Yr n): Sol 150 mg (2.6% to 4.9%; base case 3.7%)	£34,497	£33,752

Abbreviations: ESS, Epworth Sleepiness Scale; ICER, incremental cost effectiveness ratio; LoE, loss of efficacy;; 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 the values at which standard of care with the addition of solriamfetol would become cost-effective at a willingness to pay threshold of £20,000 or £30,000 per QALY. In this analysis, all other parameters were maintained at their original value. As with the univariate analysis, the threshold analysis was performed on the TONES 3 mIPD. Results of the threshold analysis are presented in Table 39.

Table 39. Results of threshold analysis: standard of care with the addition of solriamfetol versus standard of care without solriamfetol

Variable	Base case	Value to achieve ICER of:	
	(Lower bound – Upper bound)	£20,000 per QALY	£30,000 per QALY
NHWS mapping - ESS Score: 12-24 coeff	-0.01309 ([redacted] to -[redacted])	-0.02343*	-0.01510
Discount rate: Costs	3.5% (0.0% to 6.0%)	13.5%*	5.4%
Discount rate: Outcomes	3.5% (0.0% to 6.0%)	-2.3%*	1.9%
Proportion of patients on Sol 37.5 mg	40.0% (20.0% to 60.0%)	69.6%†	50.3%
Proportion of patients on Sol 75 mg	40.0% (20.0% to 60.0%)	83.5%†	56.1%
NHWS mapping - ESS Score: 0-11 coeff	-0.00263 ([redacted] to [redacted])	-0.01989*	-0.00598*
Discontinuation - LoE (Yr 1): Sol 150 mg	3.6% (1.8% to 5.4%)	-17.9%*	-4.6%*
Discontinuation - LoE (Yr n): Sol 37.5 mg	3.6% (1.8% to 5.4%)	NA	39.1%*
Discontinuation - TEAEs (Yr n): Sol 37.5 mg	3.7% (2.6% to 4.9%)	-17.0%*	-3.9%*
Discontinuation - TEAEs (Yr n): Sol 150 mg	3.7% (2.6% to 4.9%)	NA	39.7%*

Abbreviations: coeff, coefficient; ESS, Epworth Sleepiness Scale; ICER, incremental cost effectiveness ratio; LoE, loss of efficacy; NHWS, National Health and Wellness Survey; QALY, quality adjusted life year; TEAE, treatment emergent adverse events; Yr 1, Year one; Yr n, Years 2 and beyond.
* Outside credible range.
† Because the other doses are varied independently these scenarios are implausible (as the total share will exceed 100%).

In this analysis when parameters were considered individually, and all other parameters remained unchanged, for the ICER for solriamfetol versus standard of care to increase to £30,000 per QALY:

- The NHWS mapping coefficient for ESS score between 0-11 and 12-24 had to change [redacted]
- The discount rate for costs would need to increase to 5.4% or the discount rate for outcomes would need to decrease to 1.9%
- The proportion of patients on 37.5 mg could increase to 50.3% or for 75 mg could increase to 56.1%. Note that in these instances the proportion of patients on 150 mg changes to ensure all three doses total to 100%
- All discontinuation rates were outside of defined credible ranges

Note that the Excel Goal Seek functionality used to perform the threshold analysis can generate illogical answers, although mathematically correct, e.g. negative discontinuation rates. All such illogical outcomes have been indicated in the respective tables.

B.3.8.4 Scenario analysis

B.3.8.4.1 Alternative model time horizon

As OSA is a chronic condition, the base case analysis assumed a lifetime horizon. For completeness, a scenario analysis considering alternative time horizons was conducted (Table 40). This analysis demonstrates that the impact of varying the time horizon is minimal and does not alter the cost-effectiveness results.

Table 40. Scenario analysis: Alternative model time horizon

Time horizon	Solriamfetol			
	37.5 mg	75 mg	150 mg	Weighted
5	£19,124	£37,171	£49,847	£35,340
10	£18,470	£35,893	£49,385	£34,501
15	£18,290	£35,543	£49,257	£34,270
20	£18,217	£35,402	£49,205	£34,177
25	£18,184	£35,338	£49,181	£34,134
30	£18,169	£35,310	£49,171	£34,116
35	£18,163	£35,299	£49,167	£34,108
40	£18,162	£35,296	£49,165	£34,106
45	£18,161	£35,295	£49,165	£34,106
50	**£18,161**	**£35,295**	**£49,165**	**£34,106**

B.3.8.4.2 Alternative definition of response

The literature indicates a reduction in ESS scores of between 2–4 is a clinically relevant change in the level of EDS (110-112), and UK KOL Evidence suggests scores of 2–4 are considered reasonable although there is variability in the use of ESS in practice (with no consensus on a definition of 'response' based on absolute ESS reduction) (51). It was therefore considered reasonable that the base case analysis used a midpoint value and assumed that 'response' was an ESS reduction of ≥3 points (175), with scenarios using an ESS reduction of ≥2 or ≥4 presented in Table 41 and Table 42, respectively. The results showed that alternative definitions of response have minimal impact on the incremental ICER, demonstrating that the results are robust and support the base case assumptions.

Table 41. Scenario analysis: Response is a reduction in ESS ≥2 – Combined

Technologies	Total costs (£)	Total QALYs	LYG	Incremental costs (£)	Incremental QALYs	Incremental ICER
Standard of care without solriamfetol	£0	11.054	29.280			
Standard of care with the addition of solriamfetol	£8,328	11.293	29.280	£8,328	0.239	£34,873

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

Table 42. Scenario analysis: Response is a reduction in ESS ≥4 – Combined

Technologies	Total costs (£)	Total QALYs	LYG	Incremental costs (£)	Incremental QALYs	Incremental ICER
Standard of care without solriamfetol	£0	11.054	29.280			
Standard of care with the addition of solriamfetol	£5,905	11.236	29.280	£5,905	0.182	£32,482

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

B.3.8.4.3 True placebo response for standard of care without solriamfetol

As noted in Section B.3.3.2, the base case analysis assumed that all of the efficacy in the placebo arm of TONES 3 is due to the Hawthorne effect. However, it is possible that some of the effect is a true placebo. The following scenario uses the unadjusted mIPD from TONES 3 for the three doses of solriamfetol and assumes

that those patients on standard of care, who received no active treatment for their EDS, maintain their baseline level of EDS for the entire model duration. As could be expected, this scenario improves the ICER for solriamfetol (Table 43).

Table 43. Scenario analysis: True placebo response for standard of care without solriamfetol

Technologies	Total costs (£)	Total QALYs	LYG	Incremental costs (£)	Incremental QALYs	Incremental ICER
Standard of care without solriamfetol	£0	11.054	29.280			
Standard of care with the addition of solriamfetol	£11,892	11.437	29.280	£11,892	0.383	£31,047

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

With an improved efficacy, relative to standard of care, the number of responders with solriamfetol increases resulting in an increase in incremental costs, from £7,402 to £11,892, and incremental QALYs raising from 0.217 to 0.383. In reality it is likely that the actual placebo effect seen in TONES 3 is a combination of both the Hawthorne and true placebo mechanisms therefore the ICER will lie between the base case ICER of £34,106 and the £31,047 ICER demonstrated in this scenario.

B.3.8.4.4 Disaggregated results utilising bootstrapping methods

Due to the relatively small sample size for each solriamfetol dose in TONES 3, the base case analysis was conducted utilising bootstrapping methods, as detailed in Section B.3.3.3 and using a dose split of 40/40/20. The results are presented in Table 44, and are highly congruent with the base case results presented in Table 35.

Table 44: Results of the bootstrapping analysis on the raw mIPD – dose split 40/40/20

Technologies	Total costs (£)	Total QALYs	Total LYG	Incremental costs versus baseline (£)	Incremental QALYs versus baseline	ICER versus baseline (£/QALY)
Standard of care without solriamfetol	£0 (£0 - £0)	11.135 (11.126 - 11.144)	29.641 (29.602 - 29.679)			
Standard of care with solriamfetol 37.5 mg	£3,241 (£3,202 - £3,279)	11.314 (11.305 - 11.323)	29.641 (29.602 - 29.679)	£3,241	0.179	£18,114

Technologies	Total costs (£)	Total QALYs	Total LYG	Incremental costs versus baseline (£)	Incremental QALYs versus baseline	ICER versus baseline (£/QALY)
Standard of care with solriamfetol 75 mg	£6,929 (£6,852 - £7,006)	11.332 (11.323 - 11.341)	29.641 (29.602 - 29.679)	£3,688	0.018	£35,160
Standard of care with solriamfetol 150 mg	£16,876 (£16,795 - £16,956)	11.479 (11.470 - 11.488)	29.641 (29.602 - 29.679)	£9,947	0.147	£49,106

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

B.3.8.4.5 Alternative solriamfetol dose split

Data from the US suggest a [redacted] dose split for the 37.5, 75 and 150 mg doses of solriamfetol, respectively, but it is anticipated that UK prescribers will be more conservative compared with those in the US, leading to an estimated 40/40/20 dose split of solriamfetol 37.5 mg, 75 mg and 150 mg. The base case analysis (combined solriamfetol) assumed this 40/40/20 split.

The disaggregated results for standard of care with the addition of solriamfetol 37.5 mg, 75 mg and 150 mg resulted in ICERs for each individual dose of £18,114, £35,160 and £49,106 respectively, versus standard of care without solriamfetol (Table 45).

Table 45: Disaggregated solriamfetol results by solriamfetol dose

Technologies	Total costs (£)	Total QALYs	Total LYG	Incremental costs versus baseline (£)	Incremental QALY versus baseline	ICER versus baseline (£/QALY)
Standard of care without solriamfetol	£0	11.054	29.280			
Standard of care with solriamfetol 37.5 mg	£3,206	11.230	29.280	£3,206	0.177	£18,161
Standard of care with solriamfetol 75 mg	£6,866	11.248	29.280	£6,866	0.195	£35,295
Standard of care with solriamfetol 150 mg	£16,867	11.397	29.280	£16,867	0.343	£49,165

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

However, due to the highly individual nature of EDS (80), it is expected that the final dose split will vary in UK clinical practice. Consequently, the ICER for standard of care with the addition of solriamfetol compared with standard of care without solriamfetol may change according to the solriamfetol dose split applied. Given that lower doses of solriamfetol may be used more frequently in the UK, this would consequently result in lower overall ICERs however, the ICERs will fall within the range of £18,161 to £49,165 per QALY reported for the individual solriamfetol doses in Table 45.

For completeness, dose split scenarios have been presented to show the alternative ICERs resulting from a 33/33/33 and 25/50/25 dose split for solriamfetol 37.5 mg, 75 mg and 150 mg and presented in Table 46 and Table 47, respectively.

Table 46. Alternative solriamfetol dose split: 37.5 mg -33%, 75 mg-33%, 150 mg-33%

Technologies	Total costs (£)	Total QALYs	LYG	Incremental costs (£)	Incremental QALYs	Incremental ICER
Standard of care without solriamfetol	£0	11.054	29.280			
Standard of care with the addition of solriamfetol	£8,980	11.292	29.280	£8,980	0.238	£37,723

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

Table 47. Alternative solriamfetol dose split: 37.5 mg -25%, 75 mg-50%, 150 mg-25%

Technologies	Total costs (£)	Total QALYs	LYG	Incremental costs (£)	Incremental QALYs	Incremental ICER
Standard of care without solriamfetol	£0	11.054	29.280			
Standard of care with the addition of solriamfetol	£8,451	11.281	29.280	£8,451	0.227	£37,203

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

As solriamfetol represents the only licensed treatment option for the management of EDS in patients with OSA whose EDS has not been satisfactorily treated by a primary OSA therapy, it is difficult for KOLs to anticipate the final dose mix of

solriamfetol. However it is expected that in clinical practice solriamfetol titration will be specific to the individual patient, consistent with the individual nature of the impact of EDS, and solriamfetol will be titrated to the lowest dose that achieves optimal effect on EDS. Based on the IPD from TONES 3 (Table 28), responders to each dose of solriamfetol will achieve similar reductions in ESS scores, however the proportion of responders increases at higher doses. Based on this evidence, it is expected that only patients who do not respond optimally to a lower dose of solriamfetol would titrate to a higher dose, where the definition of optimal is specific to each patient due to the individual nature of EDS. Furthermore, modafinil was previously indicated to manage EDS due to OSA, but the EMA removed this indication in 2010 following a review procedure which concluded that the benefits of modafinil-containing medicines do not outweigh the risks in the OSA population (92). It is therefore expected that clinicians would titrate solriamfetol cautiously, until they experience the well-characterised safety profile of solriamfetol first-hand.

B.3.8.4.6 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.

B.3.8.4.6.1 OSA based QoL estimates from McDaid

McDaid 2007 (76) used the surrogate end point of ESS score as a proxy for differences in utility. Their analysis used three sets of IPD (two measuring ESS and SF-36 profile in the same patients, and 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 SF-6D values (based on tariffs published by Brazier 2002 (176) and Dolan 1995 (177)) using linear regression analyses. The results of this process indicated that a unit fall in ESS score for a patient with OSA is associated with an increase in utility value of 0.0095 (95% CI 0.0070 to 0.0123) based on SF-6D (n=294), and an increase in utility value of 0.0097 (95% CI 0.0019 to 0.0175) based on EQ-5D-3L (n=94). A scenario analysis that utilised the ESS to EQ-5D regression analysis from McDaid 2007 is presented in Table 48. The results of this scenario analysis are highly

congruent with the base case analysis, with a slight increase in the incremental QALYs associated with solriamfetol resulting in a lower ICER of £32,248 per QALY.

Table 48. Scenario analysis: ESS to EQ-5D McDaid 2007 regression - Combined

Technologies	Total costs (£)	Total QALYs	LYG	Incremental costs (£)	Incremental QALYs	Incremental ICER
Standard of care without solriamfetol	£0	13.814	29.280			
Standard of care with the addition of solriamfetol	£7,402	14.044	29.280	£7,402	0.230	£32,248

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

B.3.8.4.6.2 OSA based QoL estimates from TTO analysis

A scenario analysis utilising the patient TTO analysis reported in Section B.3.4.4.2 is presented in Table 49. Utilising the TTO analysis results in a substantial increase in the incremental QALYs associated with solriamfetol compared to standard of care. The resulting ICER is £14,168 per QALY.

Table 49. Scenario analysis: TTO utilities - Combined

Technologies	Total costs (£)	Total QALYs	LYG	Incremental costs (£)	Incremental QALYs	Incremental ICER
Standard of care without solriamfetol	£0	12.326	29.280			
Standard of care with the addition of solriamfetol	£7,402	12.848	29.280	£7,402	0.522	£14,168

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

B.3.8.4.6.3 Partner utilities

As described in Sections B.1.3 and B.3.4.4.2, the impact of EDS due to OSA can extend beyond the patient and negatively impact their partner's HRQoL. Due to a combination of factors including, the impact of EDS on the patient-partner relationship, the family dynamic, ability to help with housekeeping, and childrearing, there is a substantial disutility to the partner of a patient with EDS due to OSA which is not typically considered when assessing the impact of treatment in clinical practice. While the true and absolute impact of EDS due to OSA on the patient's partner is difficult to assess robustly, a scenario analysis utilising the relationship

between patient and partner utilities as identified in the TTO analysis ([redacted]) was used to assess the impact of the partner utility on the overall ICER. The health states used to elicit these partner utility values are described in further detail in Section B.3.4.4.2 and Appendix N. To provide a comprehensive perspective of the impact of the partner burden due to EDS on the cost-effectiveness of solriamfetol, the impact on partner utility was applied to each of the three alternative sources of utility estimates (NHWS mapping, McDaid mapping, and TTO analysis).

As described in Section B.3.4.4.3, for each analysis it was assumed that 66% of patients would be living as a couple and thus have partners who could be affected by their EDS. For simplicity, it was assumed that the partner would be the same age, and die at the same rate as the patient, using the standard life tables. The results of this analysis describing the cost-effectiveness of solriamfetol when accounting for the impact of EDS on partners, are presented in Table 50 to Table 52. In all scenarios the incremental QALYs are increased by around 35% when considering the partner utility, which consequently reduced the ICER significantly from each of the respective scenarios when not considered the effect of partner utilities.

Of note, including the impact of EDS on the partner contributes substantial cost-effectiveness to solriamfetol, with ICERs below or near the £20,000 threshold. Due to the health states considered in the study, the TTO scenario likely represents an overly favourable ICER for solriamfetol, however, the similar ICERs for the NHWS and McDaid datasets strongly suggests based on an average of these two ICERs that the ICER for standard of care with the addition of solriamfetol vs standard of care without solriamfetol, when considering the partner utility will be near £25,000.

Table 50. Scenario analysis: NHWS mapping combined with partner utilities

Technologies	Total costs (£)	Total QALYs	LYG	Incremental costs (£)	Incremental QALYs	Incremental ICER
Standard of care without solriamfetol	£0	19.869	29.280			
Standard of care with the addition of solriamfetol	£7,402	20.166	29.280	£7,402	0.297	£24,923

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; NHWS, National Health and Wellness Survey; QALYs, quality-adjusted life years.

Table 51. Scenario analysis: McDaid mapping combined with partner utilities

Technologies	Total costs (£)	Total QALYs	LYG	Incremental costs (£)	Incremental QALYs	Incremental ICER
Standard of care without solriamfetol	£0	23.647	29.280			
Standard of care with the addition of solriamfetol	£7,402	23.961	29.280	£7,402	0.314	£23,566

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

Table 52. Scenario analysis: TTO patient utilities combined with TTO partner utilities

Technologies	Total costs (£)	Total QALYs	LYG	Incremental costs (£)	Incremental QALYs	Incremental ICER
Standard of care without solriamfetol	£0	21.610	29.280			
Standard of care with the addition of solriamfetol	£7,402	22.325	29.280	£7,402	0.715	£10,353

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

B.3.8.5 Summary of sensitivity analyses results

The results of PSA were highly congruent with the deterministic base case results and showed standard of care with the addition of solriamfetol to be cost-effective versus standard of care without solriamfetol in 34% of simulations, assuming a cost-effectiveness threshold of £30,000 per QALY.

The most influential parameters in deterministic sensitivity analysis were the discount rates for costs and outcomes, the proportion of patients on the 37.5 mg or 75 mg formulations of solriamfetol, and the NHWS mapping coefficients associated with ESS. The effects of other model parameters on the base case ICER were found to be modest and the extensive scenario analyses presented above have demonstrated the robustness of the base case ICER.

The inclusion of the impact on quality of life of the partner also demonstrated the conservative base case position for a disease area with significant societal impact.

B.3.9 Subgroup analysis

B.3.9.1 Compliant or non-compliant to primary OSA therapy

Patients in TONES 3 were randomised to receive solriamfetol or placebo, stratified according to compliant or non-compliant use of a primary OSA therapy (Table 4):

- Compliant use of a primary OSA therapy was defined as PAP use of ≥4 hours per night on ≥70% of nights (≥5 of 7 nights/week), a historical report (with investigator concurrence) of use of an oral appliance on ≥70% of nights (≥5 of 7 nights/week), or receipt of an effective surgical intervention for OSA symptoms.
- Non-compliant use of a primary OSA therapy was defined as use of CPAP, an oral appliance, or an upper airway stimulator at a frequency or duration less than that described above, no use of a primary OSA therapy, or receipt of a surgical intervention that was no longer effective in the absence of compliant PAP or oral appliance use.

Note that [redacted] patient with a history of using a primary OSA therapy was not currently using a primary OSA therapy during TONES 3, therefore [redacted] in the non-compliant subgroup met one of the other criteria for non-compliance (i.e. use of a primary OSA therapy at a frequency/duration less than that described above, or receipt of a surgical intervention that was no longer effective in the absence of compliant PAP or oral appliance use).

The base case analysis made no distinction between compliant or non-compliant use of a primary OSA therapy, but for completeness the respective subgroups were considered here. The results of these analyses, presented in Table 53 and Table 54, demonstrated that limiting the analysis to either patients who were compliant or non-compliant to their primary OSA therapy did not change the conclusion of the base case analysis.

Table 53. Scenario analysis: Compliant to a primary OSA therapy (at randomisation into TONES 3) – solriamfetol combined

Technologies	Total costs (£)	Total QALYs	LYG	Incremental costs (£)	Incremental QALYs	Incremental ICER
Standard of care without solriamfetol	£0	11.151	29.262			

Technologies	Total costs (£)	Total QALYs	LYG	Incremental costs (£)	Incremental QALYs	Incremental ICER
Standard of care with the addition of solriamfetol	£7,052	11.346	29.262	£7,052	0.194	£36,311

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

Table 54. Scenario analysis: Non-compliant to a primary OSA therapy (at randomisation into TONES 3) – solriamfetol combined

Technologies	Total costs (£)	Total QALYs	LYG	Incremental costs (£)	Incremental QALYs	Incremental ICER
Standard of care without solriamfetol	£0	11.221	31.074			
Standard of care with the addition of solriamfetol	£8,428	11.502	31.074	£8,428	0.281	£29,991

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

B.3.9.2 Baseline ESS at entry

The base case analysis assumed that all patients with an ESS score >10 would be considered eligible for solriamfetol treatment. A scenario analysis was conducted to determine the impact on cost-effectiveness of including only those patients with higher baseline ESS scores (ESS>12; Table 55). To facilitate this analysis, all patients who had a baseline ESS ≤12 were excluded from the mIPD. In doing so approximately 25% of all patients were excluded from the analysis.

As for the base case analysis, a weighted ICER is presented in Table 55, which assumed a 40/40/20 split for the 37.5 mg, 75 mg and 150 mg doses of solriamfetol, respectively. In this analysis the ICER for standard of care with the addition of solriamfetol versus standard of care without solriamfetol decreased with each unit change in baseline ESS, such that when prescribing solriamfetol treatment only to patients with a baseline ESS >12 the weighted ICER was £29,104 per QALY.

Table 55. Incremental ESS scores considered from the TONES 3 mIPD

Baseline ESS	37.5 mg	75 mg	150 mg	Weighted
>10 (base case)	£18,161	£35,295	£49,165	£34,106
>12	£15,508	£29,955	£41,798	£29,014

Abbreviations: ESS, Epworth sleepiness scale; IPD, individual patient data; mIPD, modified individual patient data; OSA, obstructive sleep apnoea.

B.3.9.3 Variable baseline ESS at entry by dose

As noted in the alternative dose split scenario analysis (Section B.3.8.4.5), solriamfetol represents the only licensed treatment option for the management of EDS in patients with OSA whose EDS has not been satisfactorily treated by a primary OSA therapy. As solriamfetol is the only treatment currently licensed in this indication, it is difficult to determine how solriamfetol will be used in clinical practice. It is expected the in UK pracitce, patients with EDS due to OSA will be titrated to the lowest effective dose for optimal efficacy, where the definition of optimal is specific to each patient, due to the individual nature of EDS.

Based on this KOL Evidence, scenario analysis applying variable baseline ESS scores for each dose of solriamfetol was conducted. Table 56 presents a scenario where the solriamfetol 37.5, 75 and 150 mg doses were only used in patients with baseline ESS scores of ESS >10, ESS >12 and ESS >14 points, respectively. This analysis utilised the 40/40/20 dose split that was applied in the base case analysis.

Table 56. Subgroup analysis: 37.5 mg (ESS >10), 75 mg (ESS >12), 150 mg (ESS >14)

Technologies	Total costs (£)	Total QALYs	LYG	Incremental costs (£)	Incremental QALYs	Incremental ICER
Standard of care without solriamfetol	£0	10.974	29.823			
Standard of care with the addition of solriamfetol (40/40/20: 37.5, 75, and 150 mg)	£8,235	11.259	29.823	£8,235	0.285	£28,909

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

For the analysis, the corresponding standard of care without solriamfetol data was used to account for the variable subgroups selected for each individual solriamfetol dose. For example, patients with a baseline ESS >10 in the solriamfetol 37.5 mg arm were compared with the corresponding data for standard of care without solriamfetol (i.e. patients with baseline ESS >10 in the placebo arm), and those with a baseline ESS >12 in the solriamfetol 75 mg arm were compared with the corresponding

dataset for standard of care without solriamfetol (i.e. patients with a baseline ESS >12 in the placebo arm).

In this analysis, the ICER for standard of care with the addition of solriamfetol versus standard of care without solriamfetol was below the £30,000 per QALY threshold. This subgroup analysis represents the expected clinical use of solriamfetol, which is anticipated to have a varied split of final solriamfetol doses used across a range of patient levels of EDS (with variable baseline ESS at the point of initial assessment for solriamfetol eligibility). These results demonstrated a reduction of £5,197 compared with the base case ICER of £34,106.

B.3.10 Validation

B.3.10.1 Validation of cost-effectiveness analysis

For 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 the pharmacological management of adult patients with EDS due to OSA, per the current decision problem (Table 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 UK KOL Evidence (51, 90).

The health economic analysis was driven predominantly by the drug costs associated with solriamfetol, and the respective reductions in ESS from baseline, compared with standard of care, the value for which were derived from the pivotal TONES 3 RCT. One of the key drivers in the cost effectiveness of solriamfetol was the final mix of doses for solriamfetol. As solriamfetol represents the only licensed

treatment option for the management of EDS in patients with OSA whose EDS has not been satisfactorily treated by a primary OSA therapy, and the study design in TONES 3 utilised a forced titration approach, it is difficult to determine how the individual doses of solriamfetol may be used in UK clinical practice. To assess the impact of a variety of dose splits and baseline ESS criteria, extensive scenario analyses on dose splits and patient subgroups (as defined by baseline ESS) were performed and demonstrated the robustness of the base case ICER.

The cost-effectiveness analysis was performed using ESS scores, which is used in UK clinical practice to assess response to treatment in patients with EDS due to OSA (51). Using this particular outcome measure may have underestimated the true cost-effectiveness of solriamfetol as the efficacy analyses using the objective MWT demonstrated a more significant improvement for solriamfetol versus placebo than was demonstrated by the ESS (Section B.2.6.1.2). Accordingly, the current analysis for assessing cost-effectiveness using ESS can be considered a conservative approach.

In addition to the significant impact on quality of life to the patient, the incremental impact to partners can also be substantial, such that the partners of patients with OSA may urge the patient to seek help for their condition, and may report substantial detriment to their relationship as a result of OSA-related symptoms. By incorporating the impact of EDS due to OSA on the partner's HRQoL into the current analysis, the results demonstrated further cost-effectiveness of solriamfetol than was observed when considering only the patient's QoL.

In current clinical practice, patients with EDS due to OSA currently have no option other than to continue to tolerate their persistent, disabling, and burdensome EDS. Unfortunately, the significance and impact of EDS due to OSA is often under recognised in comparison to the patient's underlying OSA, despite the widely accepted burden and impact of EDS in other indications, such as patients with EDS due to narcolepsy. These patients have a clear unmet need for treatment to manage their EDS, with UK KOLs reporting that EDS is extremely disabling; furthermore, KOLs use terms such as "hugely", "immense" and "massive" when describing how patients value having their EDS managed, demonstrating the importance of having

an effective treatment option for managing EDS due to OSA. The base case analysis demonstrated that solriamfetol as an add-on treatment to standard of care is cost-effective versus the only comparator, standard of care without solriamfetol (i.e. primary OSA therapies for the underlying cause of OSA). As such, solriamfetol offers a cost-effective use of NHS resources, in a difficult to treat patient population who have a significant unmet need for treatment of their EDS due to OSA.

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Appendices

Appendix C: Summary of product characteristics and European public assessment report

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: National health and wellness survey analysis

Appendix N: Time trade off study analysis

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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

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

Clarification question responses

24th June 2020

File name	Version	Contains confidential information	Date
ID1499 ERG Clarification_Responses_ Redacted_17Dec	3.0	Yes	17 Dec 2020

Section A: Clarification on effectiveness data

Obstructive Sleep Apnoea (OSA) treatment pathway

A1. Please define 'optimisation of standard of care' as mentioned in company submission (CS) Figure 1. Also, please confirm if optimisation of standard care would be likely to happen prior to commencing treatment with solriamfetol (it is not explicitly mentioned in the 'future pathway' section of Figure 1).

Evidence from the Sleep Services Analysis and UK KOL Interviews indicates that patients who experience persistent EDS after initiating CPAP will receive follow-up visits to increase CPAP efficacy and/or compliance (in an attempt to improve AHI, and which may also reduce EDS). Based on TA139, reasons for not adhering to CPAP treatment include poor mask fit, pressure intolerance, nasal dryness/bleeding, or throat irritation. It is widely accepted that increased compliance to CPAP may improve the treatment of OSA. During their follow-up visits, patients may receive mask refitting and/or airway pressure adjustments which may improve the patient's CPAP efficacy or compliance. Other than these changes, there are no treatment options for patients who experience persistent EDS when effectively using a primary OSA therapy (e.g. CPAP). Based on UK KOL Interviews, the degree to which these adjustments are made, how frequently and in what sequence they are made, is driven by the managing clinician's clinical judgement. These adaptations and adjustments to CPAP are considered as standard of care within the current pathway (established clinical management without solriamfetol) and do not reflect new or additional resource use.

TONES study methods and statistical approaches

A2. CS Table 11 states that the TONES 3 trial was powered to detect a 3.5-point difference in change from baseline Epworth sleepiness scale (ESS) and a 5-minute difference in change from baseline maintenance of wakefulness test (MWT) between solriamfetol and placebo. Please elaborate on how these values were chosen, and

provide any evidence that these could be considered clinically meaningful between-group differences.

These values were chosen based on two Phase 2 studies of solriamfetol that were conducted in patients with narcolepsy (there were no prior Phase 2 studies available in patients with OSA). In those studies in patients with narcolepsy, differences of 3-4 points and 4-6 points were observed on the ESS at the 150 and 300 mg doses, respectively. Differences of approximately 10 minutes were observed on the MWT at the 300 mg dose (1, 2). Differences of 3.5 points on the ESS and 5 minutes on the MWT were chosen for adequate powering of an effect at the 150 mg dose and with consideration of potential differences between the narcolepsy and OSA patient populations. A difference of 3.5 points on the ESS exceeds the minimum important difference on the ESS that has been estimated from three randomized controlled trials in OSA patients, which was proposed to be 2 (3). There have not been well-established clinically meaningful differences for the MWT; however a 5 minute difference is greater than what has been observed with other drugs (e.g. modafinil (4)) that have been approved by regulatory agencies to treat excessive daytime sleepiness associated with OSA.

A3. CS Table 11 summarises the statistical analyses used in the solriamfetol TONES trials.

a) Please confirm that the only outcomes in TONES 3 in which the fixed hierarchical testing sequence was employed were change from baseline in MWT at week 12, change from baseline in ESS at week 12, and PGI-c at week 12, with all other analyses not part of this hierarchical analysis (and thus not subject to any multiplicity adjustments).

In TONES 3, a fixed hierarchical testing sequence was used to control the family-wise error rate at 0.05 for the comparisons of the 4 solriamfetol doses versus placebo for 12-week changes from baseline in MWT, ESS and PGI-c. No other outcomes were assessed using a fixed hierarchical testing sequence. (For analyses that were not part of the prespecified hierarchical analysis, p-values presented in the text are considered nominal).

b) Please confirm that the only outcomes in TONES 4 for which the fixed hierarchical testing sequence was employed were change in MWT week 4 to

week 6, ESS week 4 to week 6 and PGI-c week 4 to week 6, with all other analyses not part of this hierarchical analysis (and thus not subject to any multiplicity adjustments).

In TONES 4, a fixed hierarchical testing sequence was used to control the family-wise error rate at 0.05 for the comparisons of the combined JZP-110 doses versus placebo for the changes from week 4 to week 6 in MWT, ESS and PGIc. No other outcomes were assessed using a fixed hierarchical testing sequence.

A4. CS appendix D.1.2 Figure 2 shows n=124 randomised patients in the double-blind withdrawal phase of TONES 4, with n=122 completing this phase and included in the modified intent to treat (mITT) population (n=62 analysed in the placebo arm and n=60 in the solriamfetol arm). In contrast, CS appendix D.1.2 Table 2 states that there were 4 participants in total who received ≥1 dose in the withdrawal phase but excluded from the mITT population (2 in the placebo arm, 1 in the 150mg solriamfetol arm and 1 in the 300mg solriamfetol arm). Please explain what appears to be a discrepancy between these two sources of information and indicate which are the correct values for the number of participants excluded from the mITT population.

CS Appendix D.1.2, Table 2 was inaccurate. The "Received ≥1 dose in the withdrawal phase but excluded from mITT population" row should equal 2 (placebo=0, solriamfetol 75 mg=0, solriamfetol 150 mg=1, solriamfetol 300 mg =1). The amended table is presented below (corrections in red):

Table 2. Population Analysis Sets, TONES 4

Population, n (%)	Total N	Placebo	Solriamfetol			
			75 mg	150 mg	300 mg	Combined
Safety Population						
Titration phase	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Stable-dose phase	157	0	23 (14.6%)	50 (31.8%)	84 (53.5%)	157 (100%)
Withdrawal phase	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Received ≥1 dose in the withdrawal phase but excluded from mITT population	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Population, n (%)	Total N	Placebo	Solriamfetol			
			75 mg	150 mg	300 mg	Combined
Did not have a baseline and post-baseline evaluation of MWT or ESS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
mITT Population	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Received ≥1 dose in the withdrawal phase but excluded from PP population	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Did Not Complete the Study†	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Had a Major Protocol Violation†	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PP population	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: CSR, Clinical study report; ESS, Epworth Sleepiness Scale, mITT, modified intent to treat, MWT, Maintenance of Wakefulness Test; PP, Per Protocol; TONES, Treatment of Obstructive sleep apnoea and Narcolepsy Excessive Sleepiness.
†One subject can have both PP Population exclusion reasons and is counted in both rows.
mITT population, Per Protocol population, and their exclusion reasons were tabulated by planned treatment, all other rows by actual treatment. A Subject's last dose level in the Titration Phase is used as treatment group in that phase.
Source: CSR Table 14.1.1.1 and 14.1.2.1b (5).

TONES study results: ESS and MWT

A5. CS Table 6 states that a reduction in ESS score of 2-3 points is considered a minimally clinically important difference (MCID). The ERG assumes this MCID refers to the change in ESS for an individual over time. Therefore, please can you justify the assumption that a >3 point difference is considered clinically meaningful when comparing the difference in mean change from baseline in ESS between solriamfetol and placebo groups? (as mentioned in CS B.2.6.1.5.1).

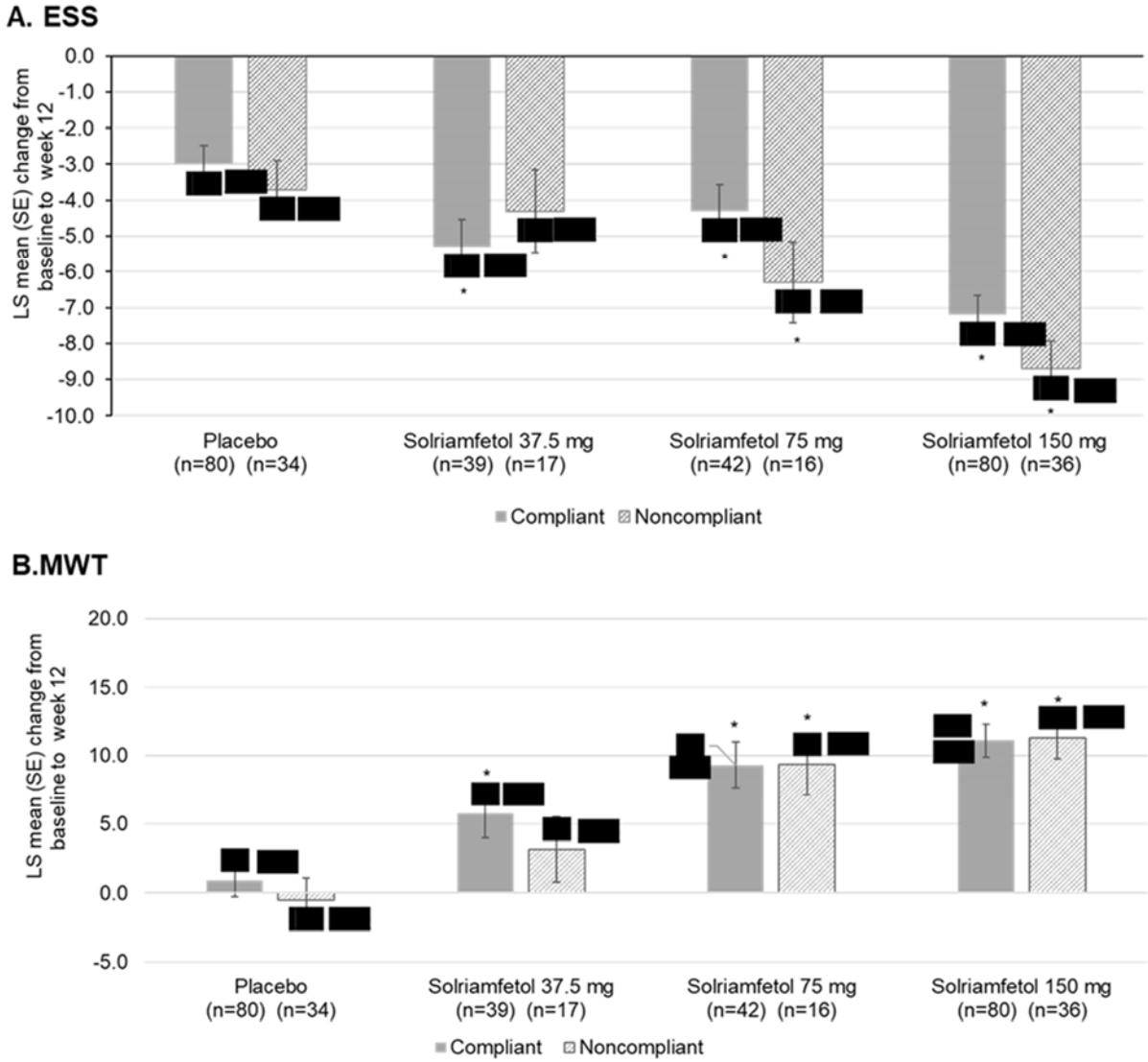
A more accurate description would be as follows:

Improvements in ESS scores for all solriamfetol doses were >4 points at all time points assessed (weeks 1, 4, 8, and 12), representing rapid, sustained and clinically meaningful improvements in EDS (based on an MCID of 2–3 points (6)).

A6. CS Figure 15 shows results of the TONES 3 compliance subgroup analysis. Please provide numerical values at baseline and for the mean change from baseline (SE) in ESS and MWT in each trial arm.

As per the Clarification Meeting, the values for LS mean and (SE) were added to Figure 15; baseline mean (SD) values are presented in the table below.

Figure 15. Subgroup analysis: MWT sleep latency and ESS change from baseline to week 12 in patients compliant or non-compliant to primary OSA therapy (mITT Population)



Abbreviations: ESS, Epworth Sleepiness Scale; LS, least squares, mITT, modified intent to treat; MWT, Maintenance of Wakefulness Test; OSA, obstructive sleep apnoea; SE, standard error.
* p<0.05 vs placebo (nominal)
Source: Schweitzer 2020 (7); CSR Table 14.2.1.1.1; Table 14.2.2.1.1 (8)..

Mean (SD) baseline values for ESS and MWT in TONES 3 (mITT Population)

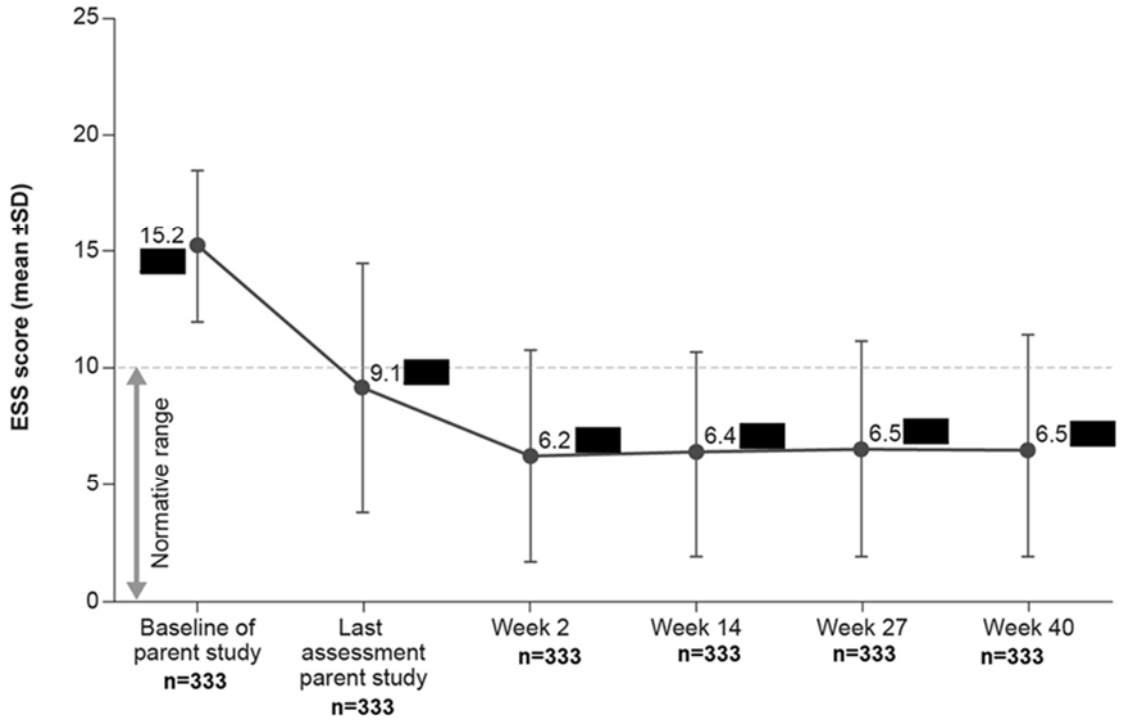
	Placebo		Solriamfetol 37.5 mg		Solriamfetol 75 mg		Solriamfetol 150 mg	
	Compliant	Noncompliant	Compliant	Noncompliant	Compliant	Noncompliant	Compliant	Noncompliant
N	80	34	39	17	42	16	80	36
Baseline, mean (SD) MWT	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Baseline, mean (SD) ESS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Source: Schweitzer 2020 (7); CSR Table 14.2.1.1.1; Table 14.2.2.1.1 (8).

A7. Please report the TONES 5 study mean (n and SD) ESS scores for patients with OSA in Group A and B at each time point assessed (as in CS Figure 8 and 9).

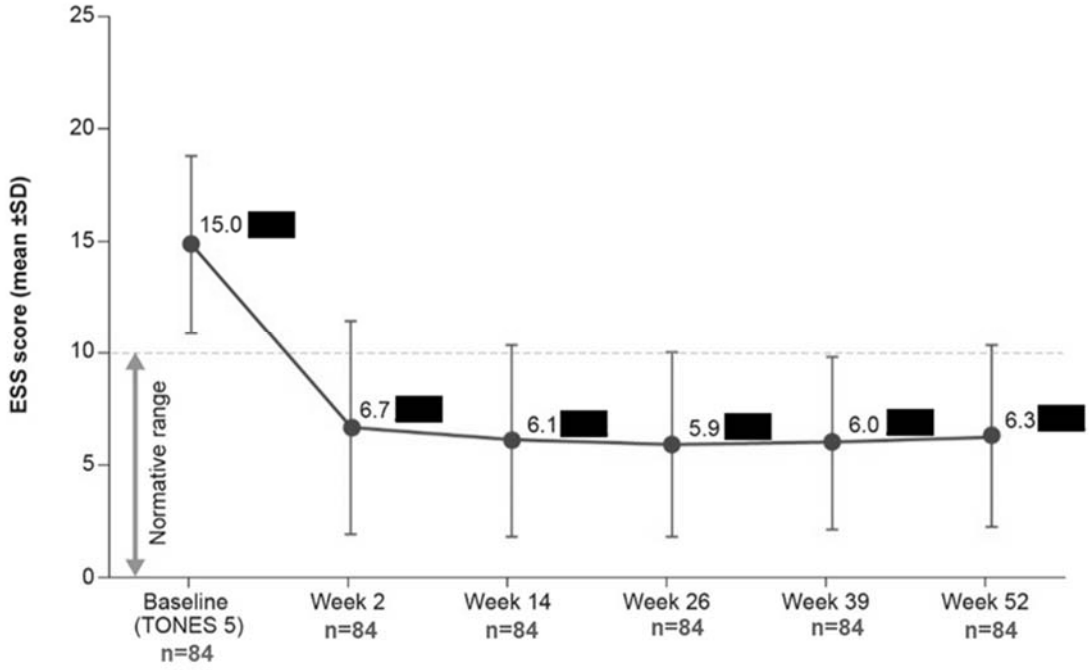
Please note that upon reviewing this question we noticed a typo in Figure 8. The mean ESS score at "baseline of the parent study" for Group A is 15.2 (per the updated figure) and not 15.9 per the original CS.

Figure 8. TONES 5: Mean (SD) ESS score for patients with OSA in Group A (n=333) 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.
*p=0.0005 vs. placebo; **p=0.0001 vs. placebo.
Source: Malhotra 2019 (9); CSR Table 14.2.1.1a (10).

Figure 9. TONES 5: Mean (SD) ESS score for patients with OSA in Group B (n=84) 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.
*p=0.0005 vs. placebo; **p=0.0001 vs. placebo.
Source: Malhotra 2019 (9); CSR Table 14.2.1.1a (10).

A8. Please report the proportion of patients in each TONES 3 study arm who achieved a reduction from baseline in ESS score of ≥ 3-points at week 12, with corresponding p-values for each pairwise comparison between groups, as per the table below.

	Placebo	**Solriamfetol 37.5 mg**	**Solriamfetol 75mg**	**Solriamfetol 150mg**
Proportion of patients with a change from baseline ESS of ≥3 at week 12	[redacted]	[redacted]	[redacted]	[redacted]
p- value for placebo vs treatment	Not applicable	[redacted]	[redacted]	[redacted]

TONES study results: Health related quality of life

A9. CS Section B.2.6.1.10 provides limited results for the EQ-5D in TONES 3. Please provide EQ-5D VAS and EQ-5D index value mean change from baseline to week 12, and mean differences (with 95% CI and p value) vs. placebo by study arm (e.g. as in CS Table 14).

The EQ-5D Index and EQ-VAS data were added to Table 14 below (data in red).

Table 14: TONES 3: HRQoL endpoints (mITT Population)

	Placebo N=114	Solriamfetol		
		37.5 mg N=56	75 mg N=58	150 mg N=116
Change in FOSQ-10 total score from baseline to week 12				
LS mean (SE)	1.72 (0.241)	1.99 (0.345)	2.47 (0.331)	2.95 (0.236)
LS mean difference vs placebo		[redacted]	[redacted]	[redacted]
95% CI		[redacted]	[redacted]	0.57, 1.88
p value		[redacted]	[redacted]	[redacted]
Change in SF-36v2 physical component summary score from baseline to week 12				
LS mean (SE)	1.43 (0.608)	1.64 (0.876)	1.99 (0.838)	3.50 (0.598)
LS mean difference vs. placebo		[redacted]	[redacted]	2.07
95% CI		[redacted]	[redacted]	0.42 to 3.72
p value (nominal)		[redacted]	[redacted]	[redacted]
Change in SF-36v2 mental component summary score from baseline to week 12				
LS mean (SE)	1.05 (0.703)	2.65 (1.012)	2.94 (0.965)	3.10 (0.691)
LS mean difference vs. placebo		[redacted]	[redacted]	2.05
95% CI		[redacted]	[redacted]	0.14 to 3.96
p value (nominal)		[redacted]	[redacted]	[redacted]
Change in EQ-5D-5L Index from baseline to week 12†				
LS mean (SE)	0.02 [redacted]	0.01 [redacted]	0.02 [redacted]	0.03 [redacted]
LS mean difference vs. placebo		[redacted]	[redacted]	[redacted]
95% CI		[redacted]	[redacted]	[redacted]
p value		[redacted]	[redacted]	[redacted]
Change in EQ-VAS from baseline to week 12				
LS mean (SE)	2.4 [redacted]	3.4 [redacted]	4.0 [redacted]	4.9 [redacted]
LS mean difference vs. placebo		[redacted]	[redacted]	[redacted]

	Placebo N=114	Solriamfetol		
		37.5 mg N=56	75 mg N=58	150 mg N=116
95% CI		[redacted]	[redacted]	[redacted]
p value		[redacted]	[redacted]	[redacted]

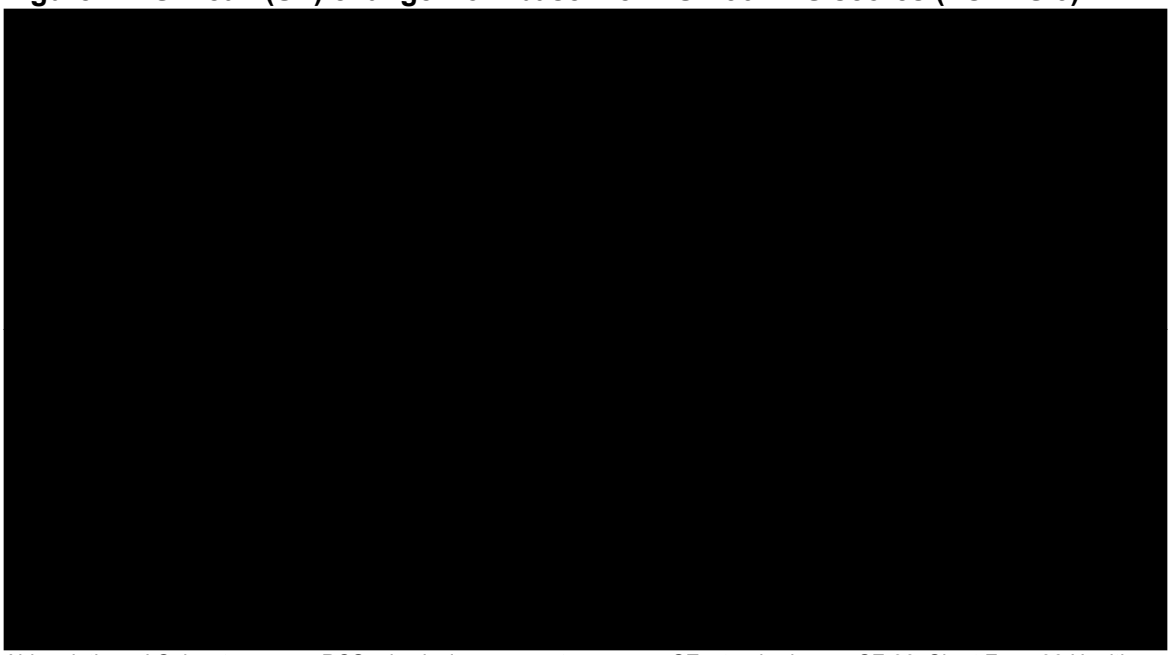
Abbreviations: CI, confidence interval; CSR, clinical study report; FOSQ-10, 10-item Functional Outcomes of Sleep Questionnaire; HRQoL, health related quality of life; LS, least squares; mITT, modified intent to treat; SD, standard deviation; SE, standard error; SF-36v2, 36-item Short-Form Health Survey version 2; TONES, Treatment of Obstructive sleep apnoea and Narcolepsy Excessive Sleepiness.
Source: Bogan 2017 (11); Benes 2017 (12); CSR Table 26, Table 14.2.7.2, Table 14.2.10.2 (8); Weaver 2020 (13).

A10. Please supply graphs showing the mean change from baseline to each follow-up point to week 12 in TONES 3 for the FOSQ-10 total score, SF-36 PCS and MCS, EQ-5D VAS and EQ-5D index score by study arm (e.g. as in Figure 5).

Figure 1. LS mean (SE) change from baseline in FOSQ-10 total score (TONES 3)

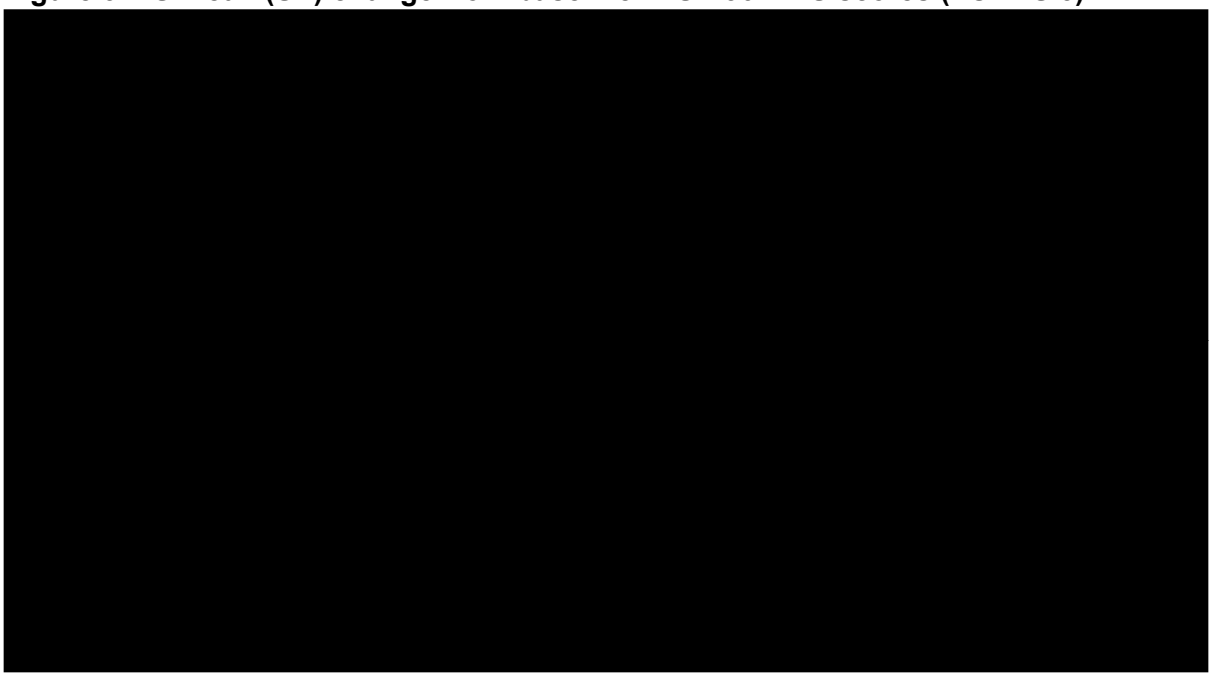
Abbreviations: FOSQ-10, Functional Outcomes of Sleep Questionnaire; LS, least squares; SE, standard error.
* p<0.05; † p<0.01 vs placebo
Source: CSR Table 26 (8); Weaver 2020 (13).

Figure 2. LS mean (SE) change from baseline in SF-36 PCS scores (TONES 3)



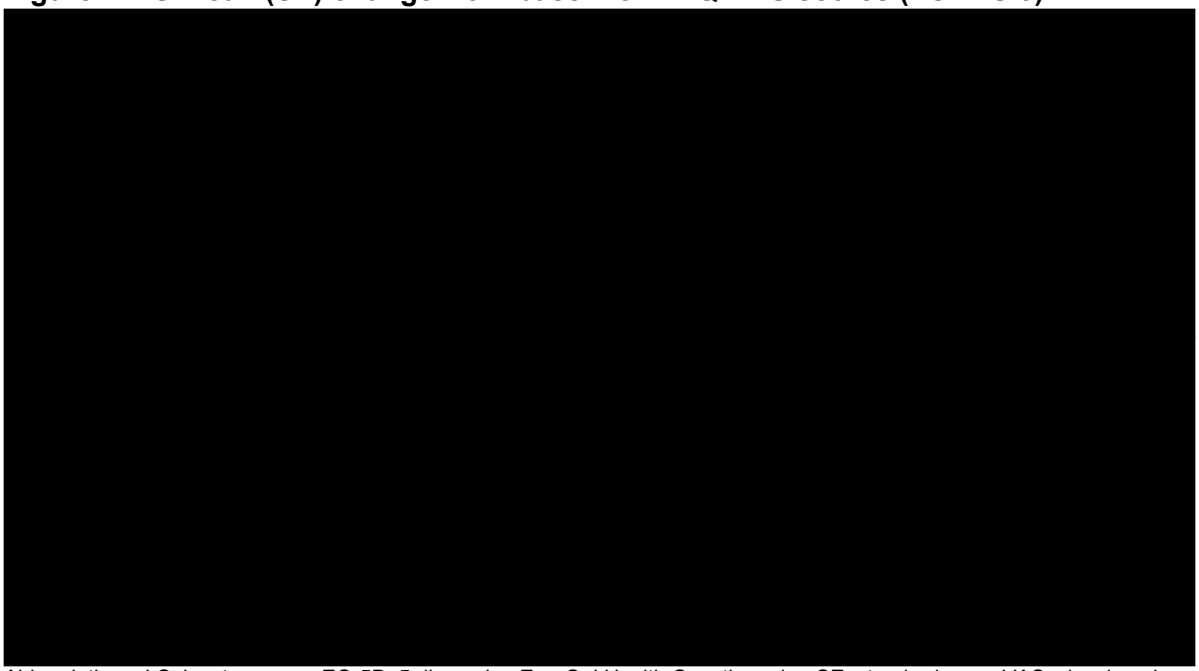
Abbreviations: LS, least squares; PCS, physical component summary; SE, standard error; SF-36, Short Form 36 Health Survey.
* p<0.05; † p<0.01 vs placebo
Source: CSR Table 14.2.7.2 (8); Weaver 2020 (13).

Figure 3. LS mean (SE) change from baseline in SF-36 MCS scores (TONES 3)



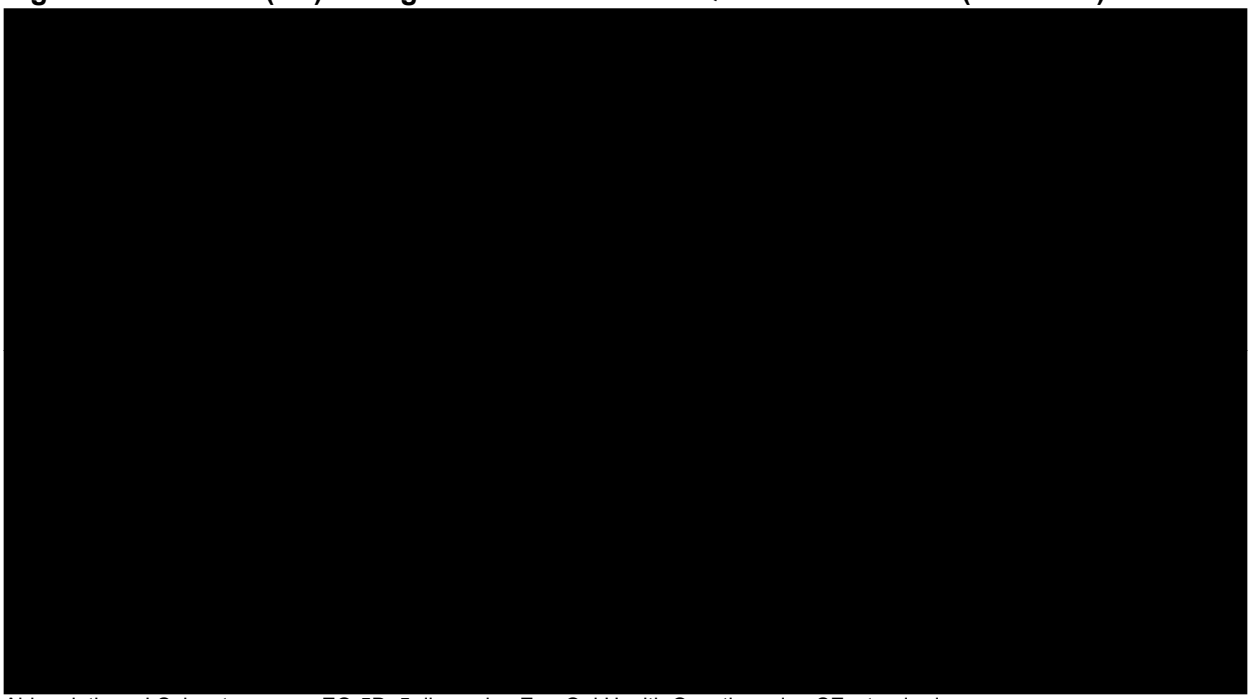
Abbreviations: LS, least squares; MCS, mental component summary; SE, standard error; SF-36, Short Form 36 Health Survey.
* p<0.05; † p<0.01 vs placebo
Source: CSR Table 14.2.7.2 (8); Weaver 2020 (13).

Figure 4. LS mean (SE) change from baseline in EQ-VAS scores (TONES 3)



Abbreviations: LS, least squares; EQ-5D, 5 dimension EuroQol Health Questionnaire; SE, standard error; VAS, visual analogue scale.
* p<0.05 vs placebo
Source: CSR Table 14.2.9.2 (8); Weaver 2020 (13).

Figure 5. LS mean (SE) change from baseline in EQ-5D Index scores (TONES 3)

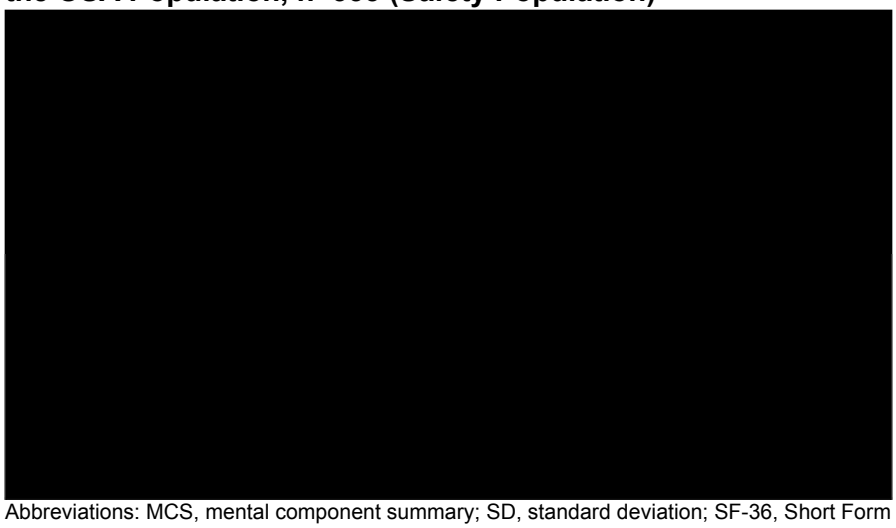


Abbreviations: LS, least squares; EQ-5D, 5 dimension EuroQol Health Questionnaire; SE, standard error.
Source: CSR Table 14.2.10.2 (8); Weaver 2020 (13).
Note that where multiple arms had the same EQ-5D Index value, the legend symbol is presented next to its LS mean (SE).

A11. Please supply graphs showing the trends in TONES 5 study SF-36 (PCS and MCS) and EQ-5D (VAS and index scores) outcomes for OSA patients over time, in the same way as for the FOSQ-10 total score in CS Figures 10 and 11.

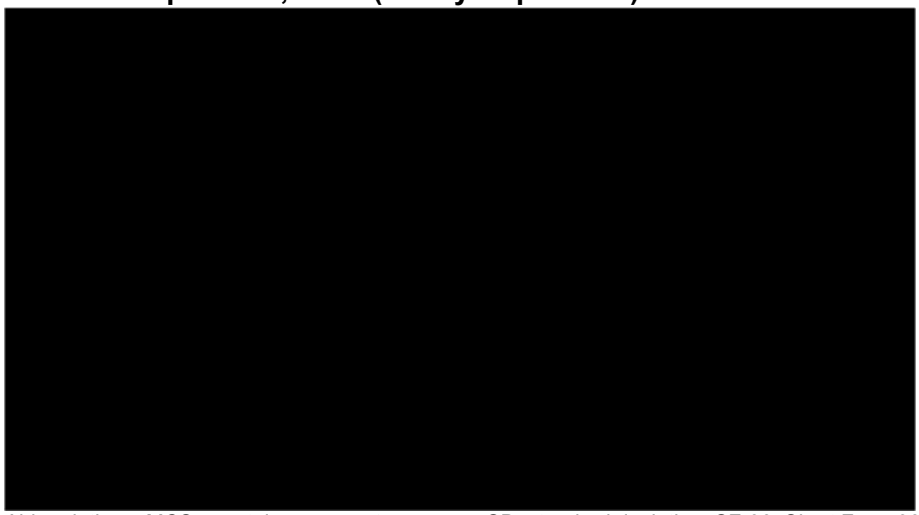
As requested, SF-36 and EQ-5D outcomes for the patients with OSA in TONES 5 are presented in the figures below:

Figure 6. TONES 5 Group A: mean (SD) SF-36 MCS scores from baseline to week 40 in the OSA Population, n=333 (Safety Population)



Abbreviations: MCS, mental component summary; SD, standard deviation; SF-36, Short Form 36 Health Survey.

Figure 7. TONES 5 Group B: mean (SD) SF-36 MCS scores from baseline to week 52 in the OSA Population, n=84 (Safety Population)



Abbreviations: MCS, mental component summary; SD, standard deviation; SF-36, Short Form 36 Health Survey.

Figure 8. TONES 5 Group A: mean (SD) SF-36 PCS scores from baseline to week 40 in the total Safety Population, n=333 (Safety Population)

Abbreviations: PCS, physical component summary; SD, standard deviation; SF-36, Short Form 36 Health Survey.

Figure 9. TONES 5 Group B: mean (SD) SF-36 PCS scores from baseline to week 52 in the total Safety Population, n=84 (Safety Population)

Abbreviations: PCS, physical component summary; SD, standard deviation; SF-36, Short Form 36 Health Survey.

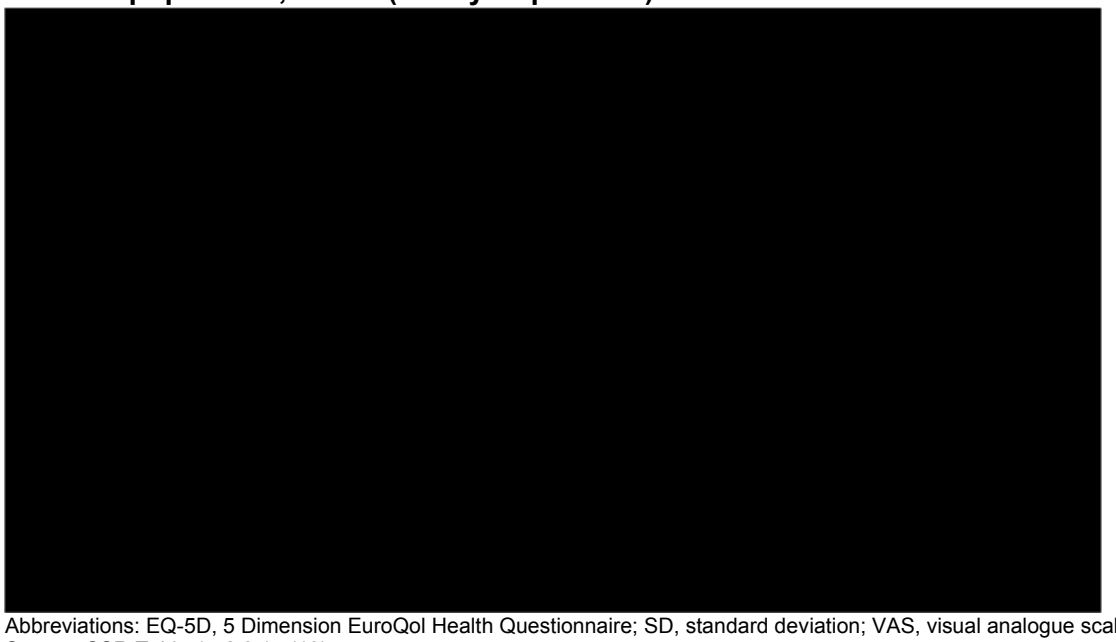
Figure 10. TONES 5 Group A: mean (SD) EQ-5D Index scores from baseline to week 40 in the OSA population, n=333 (Safety Population)

Abbreviations: EQ-5D, 5 Dimension EuroQol Health Questionnaire; SD, standard deviation.
Source: CSR Table 14.2.9.1a (10).

Figure 11. TONES 5 Group B: mean (SD) EQ-5D Index scores from baseline to week 52 in the OSA population, n=84 (Safety Population)

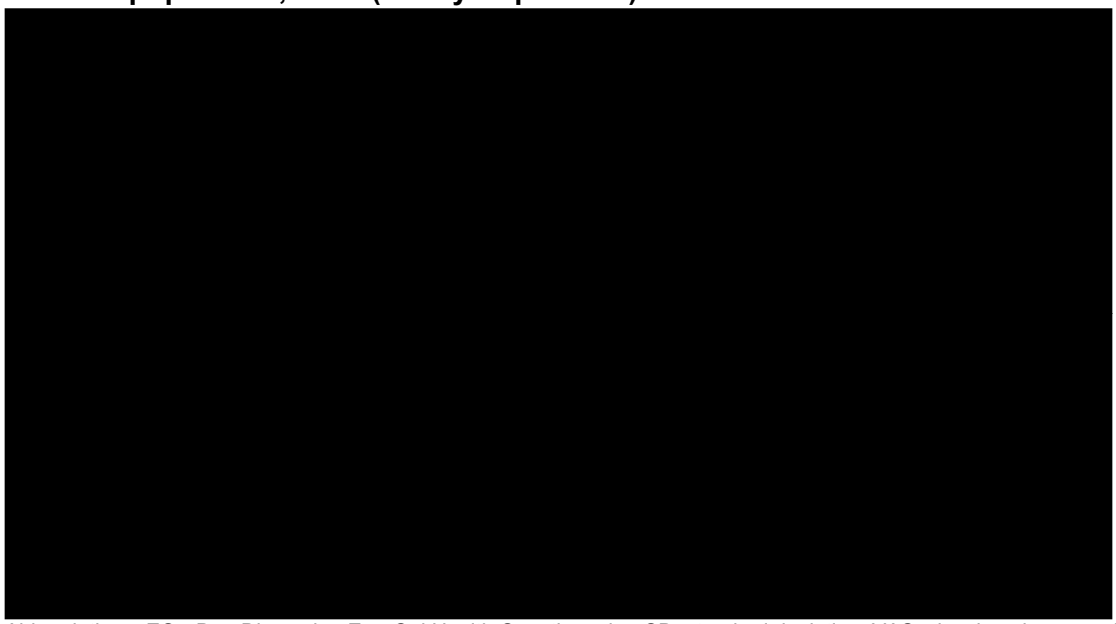
Abbreviations: EQ-5D, 5 Dimension EuroQol Health Questionnaire; SD, standard deviation.
Source: CSR Table 14.2.9.1a (10).

Figure 12. TONES 5 Group A: mean (SD) EQ-VAS scores from baseline to week 40 in the OSA population, n=333 (Safety Population)



Abbreviations: EQ-5D, 5 Dimension EuroQol Health Questionnaire; SD, standard deviation; VAS, visual analogue scale.
Source: CSR Table 14.2.8.1a (10).

Figure 13. TONES 5 Group B: mean (SD) EQ-VAS scores from baseline to week 52 in the OSA population, n=84 (Safety Population)



Abbreviations: EQ-5D, 5 Dimension EuroQol Health Questionnaire; SD, standard deviation; VAS, visual analogue scale.
Source: CSR Table 14.2.9.1a (10).

Section B: Clarification on cost-effectiveness data

Review of published cost-effectiveness studies

B1. CS Appendix G, Table 17, lists interventions for treating excessive daytime sleepiness (EDS) in people with OSA eligible for inclusion in the cost-effectiveness systematic literature review. We note that interventions such as armodafinil, histamine H3 receptor inverse agonist MK-0249 and pitolisant can also be used for this indication, but were not included in the review. Such evidence could also inform the modelling approach, assumptions and parameter estimates even if these treatments are not comparators in the decision problem. Please provide a rationale for the choice of interventions in this review.

Neither MK-0249, pitolisant nor armodafinil are indicated for use in the OSA population in Europe, and based on KOL Interviews, there is no evidence to suggest these treatments are used in England for EDS due to OSA. For completeness a new search was conducted (in response to this clarification question) combining the original disease and study design terms with the intervention terms pitolisant, armodafinil and MK-0249; this search found no relevant references that would have informed the analysis (see the below table).

Search for interventions specified in clarification question B1

Database	Intervention terms (combined with original disease and study design terms)	Total hits	Relevant hits
Embase	exp pitolisant/ OR pitolisant.mp. OR exp armodafinil/ OR armodafinil.mp. OR histamine H3 receptor agonist/ OR (MK-0249 or MK0249 or "MK 0249").mp.	18	0
MEDLINE	pitolisant.mp. OR armodafinil.mp. OR Histamine Agonists/ OR (MK-0249 or MK0249 or "MK 0249").mp.	2	0
Cochrane	As for MEDLINE	1	0

Clinical effectiveness parameters

B2. Priority question: Please provide raw IPD data (i.e. non-adjusted / non-centred data) from the TONES 3 trial for observed ESS scores at baseline and at 1, 4, 8 and

12 weeks for the solriamfetol dose arms (37.5 mg, 75 mg and 150 mg) and the placebo arm.

The TONES 3 IPD has been provided in a separate file "TONES3_IPD.xlsx".

B3. Priority question: Please explain the 'unadjusted' values reported in cells U120 to U349 of the '_IPD_OSA' sheet in the model. How do these relate to the data reported in columns G to L of this sheet?

These values were not used in the analysis directly but reflect the baseline and unadjusted week 12 values for the solriamfetol dose arms (37.5, 75, and 150 mg). The reason for including this data in the model was that the data were manually referenced when conducting the scenario analysis considering a true placebo response for SoC without solriamfetol (per CS B.3.8.4.3).

B4. Please clarify the reason for the discrepancy between CS Table 13 and the economic model (sheet '_IPD_OSA') in the mean change in ESS at 12 weeks. Table 13 reports LS mean difference vs. placebo as −1.9 −1.7 −4.5 for solriamfetol 37.5 mg, 75mg and 150mg doses respectively which are different from the values in the model.

The data in CS Table 13 represents the original clinical data for TONES 3 (for the mITT Population) whereas the model and associated analyses were based on an adjusted/centred IPD set and excluded all patients with ESS = 10 (per CS B.3.2.1).

B5. Priority question: Please clarify the reason for the difference in mean ESS (for responders and non-responders) between the model and CS Tables 28 and 31. We re-estimated the mean ESS in responders using IPD data in the model and they differed from those reported in CS Tables 28 or Table 31.

See response to B9 – The values in these tables were from the model (efficacy sheet, cells F48:K52), however in re-reviewing the tables, it was noted that the values in Table 31 were from an old iteration of the CE analysis. These have been corrected in the table below, note that this is a typographical error in the submission and does not impact the analysis presented. With these values corrected, Tables 28 and Table 31 now match both each other and the model (see below).

Please note the data in Table 31 should have been AiC and in error were not marked in the original CS, these data have now been marked as AiC.

Table 28. Clinical data utilised in the current model (OSA)

Product, daily dose	Proportion of responders (ΔESS from baseline ≥3)	Mean ESS in responders†	Mean ESS in non-responders†
Standard of care with solriamfetol 37.5 mg	[redacted]	[redacted]	[redacted]
Standard of care with solriamfetol 75 mg	[redacted]	[redacted]	[redacted]
Standard of care with solriamfetol 150 mg	[redacted]	[redacted]	[redacted]
Standard of care without solriamfetol	[redacted]	Not applicable*	[redacted]

Abbreviations: ESS, Epworth sleepiness scale; IPD, individual patient data; mIPD, modified individual patient data; OSA, obstructive sleep apnoea.
Source: TONES 3 Individual patient level data.

Table 31. Mean ESS when receiving treatment in responders and non-responders and the associated mean utilities

Product, daily dose	Mean ESS in responders	Mean utility of responders up to week 12	Mean ESS in non-responders	Mean utility in non-responders up to week 12
Standard of care with solriamfetol 37.5 mg	[redacted]	[redacted]	[redacted]	[redacted]
Standard of care with solriamfetol 75 mg	[redacted]	[redacted]	[redacted]	[redacted]
Standard of care with solriamfetol 150 mg	[redacted]	[redacted]	[redacted]	[redacted]
Standard of care without solriamfetol	Not applicable*		[redacted]	[redacted]

Abbreviations: ESS, Epworth Sleepiness Scale.
Source: TONES 3 Individual patient level data.

Cost-effectiveness model

B6. Priority question: Please provide a model update that runs the bootstrap analysis. We note that the current macro on the 'Bootstrap_Simulations' sheet links incorrectly to the PSA macro. We believe that the intended macro for executing this analysis is named "bootstrap", however, running it merely resets the results on the 'bootstrap_Results' sheet to the base case results (CS Table 35).

This was an error. The macro on the 'Bootstrap_Simulations' sheet links correctly to the "bootstrap" macro however, in preparing the model to submit, the cell selecting the base case or bootstrapped data was moved and the associated VBA code was not modified to reflect this.

To correct this error, within the boostrap macro the following lines need updates:

1. Sheets("_IPD_OSA_Summary").Range("**R6**").Value = 2

- Needs to be updated to:
- Sheets("_IPD_OSA_Summary").Range("**V6**").Value = 2

2. Sheets("_IPD_OSA_Summary").Range("**R6**").Value = 1
    - Needs to be updated to:
    - Sheets("_IPD_OSA_Summary").Range("**V6**").Value = 1

A revised version of the model has been provided with the clarification questions.

B7. Priority question: Please provide a model update that runs the scenario analyses listed in the CS. We get an error message when we click on the "Run Scenarios" button on the '_Parameters sheet'.

The majority of the scenario results have been generated manually from within the model, adjusting key parameters as required. The 'Run scenarios' button 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).

We regret any confusion this may have caused.

B8. Please clarify the proportion of patients taking the 37.5 and 75 mg doses of solriamfetol in the deterministic sensitivity analyses. It is not clear from the description given in the CS how the other doses (75 mg and 150 mg, and 37.5 mg and 150 mg, respectively) were varied in these analyses.

The model has market share inputs for the solriamfetol 37.5 and 75 mg doses with the difference from 100% comprising the proportion of patients receiving 150 mg, e.g. in the base case, 40% of patients receive 37.5 mg, 40% of patients receive 75 mg and the remainder received 150 mg (i.e. 20% = 100% - 40% [patients receiving 37.5 mg] - 40% [patients receiving 75 mg]). Within the deterministic (univariate) sensitivity analysis each parameter was varied independently, thus the ranges for the 37.5 and 75 mg doses were limited to a maximum of 60%, this ensured that when the maximum value for one dose was selected, the total could not exceed 100%, e.g. if the market share for 37.5 mg was at the maximum 60% and the market share for 75 mg was at the default 40%, the model calculated the market share for the 150 mg dose as 0% (for an overall total of 100%).

The threshold analysis utilises the Excel GoalSeek functionality to identify a single parameter value that will result in a specific output from the model, in the case of the submission an ICER value of £20,000 or £30,000 per QALY. Because this functionality is simply an iterative process within Excel, the output it produces can sometimes be illogical. With respect to the market shares of solriamfetol, the Excel GoalSeek function identified threshold values of 63.4% and 75.0% for the 37.5 mg and 75 mg doses of solriamfetol, respectively, however, because these values have been identified independently of the other doses, this resulted in a negative market share for the 150 mg formulation. For example, the GoalSeek function identified that the market share of 37.5 mg needed to be 63.4% to achieve an ICER of £20,000 per QALY when comparing solriamfetol with standard of care. However, the market share for 75 mg is set to 40% by default, thus the market share for 150 mg within the model is -3.4%, an illogical value. (100% - 63.4% [patients receiving 37.5 mg] - 40% [patients receiving 75 mg]).

Utility parameters

B9. Please clarify if the values given in CS Table 31 for mean utilities up to week 12 for responders and non-responders have been used in the model. It is not clear if/how they are used in the model.

The values presented in Table 31 are illustrative of the utility values utilised within the model; the NHWS mapping incorporates an age covariate, thus the actual values used within the model varied as the patient cohort considered age. The reference to 12 weeks was intended to indicate that this is reflective of the cohort at this timepoint and that it will vary (based on the age covariate) in subsequent analysis.

In re-reviewing the figures it was noted that the figures in Table 31 were from an old iteration of the analysis. These have been corrected in red below; note this is a typographical error in the submission and does not impact the analysis presented.

Table 31. Mean ESS when receiving treatment in responders and non-responders and the associated mean utilities

Product, daily dose	Mean ESS in responders	Mean utility of responders up to week 12	Mean ESS in non-responders	Mean utility in non-responders up to week 12
Standard of care with solriamfetol 37.5 mg	[redacted]	[redacted]	[redacted]	[redacted]
Standard of care with solriamfetol 75 mg	[redacted]	[redacted]	[redacted]	[redacted]
Standard of care with solriamfetol 150 mg	[redacted]	[redacted]	[redacted]	[redacted]
Standard of care without solriamfetol	[redacted]		[redacted]	[redacted]

Abbreviations: ESS, Epworth Sleepiness Scale.

Section C: Textual clarification and additional points

C1. In CS Table 3, the row titled 'rationale for use/non-use in the model' states that TONES 3 provides "efficacy and safety evidence for use in an indirect treatment comparison". As no indirect treatment comparison has been included please would confirm that this statement has been made in error.

Correct. This is an error.

C2. The company have indicated, in communications with NICE, that they can provide updated tables which may present some results in a clearer way. Please provide these here with clear reference to where the current tables appear in the CS.

At Clarification Stage, the company and ERG identified some typographical errors in the CS documents (table columns were labelled incorrectly, inconsistent utility values were presented between tables). These errors were corrected by the company when responding to the Clarification Questions, in order to provide clarity, and an itemised list of corrections to these typographical errors was provided here.

However NICE subsequently requested in December 2020 that all CS documents be updated and re-submitted in full. By re-submitting the CS documents, errors previously listed herein were corrected thus the itemised list became redundant and has been removed to avoid confusion (i.e. by referring to errors in the CS which no longer exist, due to NICE requesting the documents be re-submitted).

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1. 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.
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11. Bogan R, Stern T, Villa K, Chen D, Carter L, Wang H, et al., editors. Poster 110. Function and Work Productivity Measures in a Phase 3, Randomized, Placebo-Controlled, Double-Blind, Multicenter, 12-Week Study of the Safety and Efficacy of JZP-110 for the Treatment of Excessive Sleepiness in Patients With Obstructive Sleep Apnea. Sleep: 31st Annual Meeting of the Associated Professional Sleep Societies; 2017 3-7 June; Boston, MA.
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Excessive Sleepiness in Patients With Obstructive Sleep Apnea: SF-36 and EQ-5D-5L Measures. Sleep: 31st Annual Meeting of the Associated Professional Sleep Societies,; 2017 June 3-7; Boston, MA.
13. Weaver TE, Drake CL, Benes H, Stern T, Maynard J, Thein SG, et al. Effects of Solriamfetol on Quality of Life Measures From a 12-Week Phase 3 Randomized Trial. Ann Am Thorac Soc. 2020b.

NICE National Institute for Health and Care Excellence

Patient organisation submission

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

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 conditions and their treatment that is not typically available from other sources.

To help you give your views, please use this questionnaire with our guide for patient submissions.

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 10 pages.

About you	
1.Your name	[redacted]

2. Name of organisation	Sleep Apnoea Trust Association (SATA)
3. Job title or position	[redacted]
4a. Brief description of the organisation (including who funds it). How many members does it have?	SATA is a patient charity which works to improve the lives of sleep apnoea patients, their partners and their families. It is run by a small group of volunteers, almost entirely unpaid, all of whom are sleep apnoea patients. SATA is funded by subscriptions from about 1400 members.
4b. Do you have any direct or indirect links with, or funding from, the tobacco industry?	No
5. How did you gather information about the experiences of patients and carers to include in your submission?	SATA has held an annual conference (SATAday) since its inception in 1993. The SATA Committee has always regarded SATAday as an opportunity to meet members, and discuss issues, and the conferences have usually included chat-shops etc which give further opportunities for members to ask questions, provide feedback, information etc. For many years SATA ran a telephone helpline, now conducted mainly by e-mails with telephone support where essential, and we occasionally survey members or invite them to participate in surveys conducted by medical professionals. SATA is therefore confident that we have a good knowledge of the issues of concern to our members. Since this is a new technology, none of our members will have been prescribed for EDS associated with OSA, so SATA does not consider that consulting our members directly would be required.

Living with the condition	
6. What is it like to live with the condition? What do carers experience when caring for someone with the condition?	If CPAP treatment is effective, living with the condition is a matter of coping with the minor discomfort and restriction of having to sleep wearing a face mask connected by tube to a small machine, though CPAP machines are now much smaller and quieter than they were a few years ago. CPAP treatment imposes further difficulties when travelling for work or leisure in that it involves additional weight, and takes up more space, in luggage, a problem when travelling by air (and some airlines are reluctant to allow CPAP to be included in cabin baggage – which SATA regards as essential – and do not allow their use on board during long flights). Even in the UK problems often arise in hotel rooms where the plug socket is usually far away from the bed, so patients have to pack extension leads as well as their CPAP. There are minor housekeeping obligations, for example regular cleaning of masks and tubes, daily cleaning of humidifiers if used, and regular changing of filters.
Current treatment of the condition in the NHS	
7. What do patients or carers think of current treatments and care available on the NHS?	It is clear that over the past year that because all NHS staff, and in particular staff in Respiratory departments, have been desperately fighting the effects of the Covid pandemic, many sleep clinics have been able to offer only a rudimentary service during that period. Before the pandemic took hold however the majority of SATA members were very satisfied with their treatment for OSA, and the care they received from sleep clinics. Many would describe their CPAP treatment as life-changing, in terms of the dramatic improvement their day-to-day health and sense of well-being by comparison with their condition before diagnosis and treatment. That is not to say the treatment is trouble-free. Some patients have difficulty adapting to wearing a mask; some were mouth-breathers at night and cannot easily use a nasal mask, having to resort to a full-face mask or chin strap; some suffer severe panic attacks or claustrophobia. Patient access to diagnosis and treatment of OSA is erratic. SATA has monitored NHS Sleep Clinic performance for many years, and though a number of excellent sleep clinics, pre-Covid, were able to diagnose and treat patients within reasonably short wait times, too many had excessive waiting times for diagnosis, and an unreasonably long interval between diagnosis and setting patients up on CPAP

	treatment. In some cases this was due to CCGs failing to fully understand their obligation under NICE TA139 to provide adequate funding for clinics in their area of responsibility. In addition SATA considers that too many GPs do not fully understand OSA, and therefore the need to refer a patient to a sleep clinic is not necessarily their first consideration when presented with a patient's description of symptoms. In conversations with GPs at, for example, RCGP Annual Conferences, it is clear that the time in a 5-year medical degree course devoted to OSA varies between 15 minutes and an hour or so. In some of these conversations I have gained the impression that some GPs are slow to recognise symptoms in children as possibly being due to sleep disturbance, arising from OSA, and instead focus on ADHD and other similar disorders.
8. Is there an unmet need for patients with this condition?	Yes. SATA estimates that there are up to 3.9 million adults in the UK who may have OSA, with only about 0.7 million diagnosed and under treatment. SATA believes that the key to making much greater inroads into the more than 3 million undiagnosed OSA sufferers is greater understanding of OSA by the primary care sector, and also much greater GP involvement in the initial assessment, for example use by GPs of home sleep apnoea testing, eg overnight oximetry, peripheral arterial signal etc.
Advantages of the technology	
9. What do patients or carers think are the advantages of the technology?	The main technology, Continuous Positive Airway Pressure (CPAP), is recommended by NICE TA139 for treatment of patients with moderate to severe OSA, and for mild OSA where symptom affect quality of life or daily activities and lifestyle changes or other treatments are unsuccessful or inappropriate. If successful it effectively eliminates or mitigates the symptoms of OSA for most patients. SATA has no data or information on the proportion of patients with OSA who may still experience EDS, and the lack of even anecdotal evidence suggests that it only a relatively small proportion may be affected.

Disadvantages of the technology	
10. What do patients or carers think are the disadvantages of the technology?	In terms of CPAP treatment the need to wear a nasal or full-face mask whilst asleep can be restrictive and uncomfortable, and may cause panic attacks or claustrophobia, and the mask can cause irritation. Issue 1. Compliance. In terms of the technology SATA is concerned about the risk to continued compliance with CPAP, a risk highlighted by the ERG report. There is already a significant degree of non-compliance with CPAP treatment. The temptation to stop using CPAP might particularly affect patients who travel a lot (see above). To the extent that reducing or eliminating EDS by means of Solriamfetol leads to non-compliance with CPAP treatment it would not only have an impact on the overall health of patients but could undermine the cost-effectiveness case for Solriamfetol. Increased non-compliance with CPAP as a direct result of use of this technology could increase overall NHS costs for patients whose OSA who would be effectively untreated and whose previous OSA symptoms may return as a result. Current DVLA driving regulations for patients with moderate to severe OSA require them not to drive until their OSA is under control, their sleepiness is no longer excessive, *and they are complying with CPAP treatment* (my italics). Furthermore, the DVLA guidelines require patients to confirm that a review of their condition has been undertaken by a sleep clinic at least every three years for a Group 1 driver and at least annually for Group 2 drivers (bus, truck, taxi drivers etc). Though the DVLA is primarily concerned about excessive sleepiness, the guidelines nevertheless include the requirement of compliance with CPAP treatment. SATA's experience of dealings with DVLA over the past few years suggests that it would take months, if not years, to secure an amendment to the DVLA guidelines to reflect the benefits of this technology on EDS. Meanwhile, the burden on sleep clinics to undertake the annual or triennial reviews, in terms of both time and cost, would increase to the extent that use of this technology increased non-compliance with CPAP treatment, therefore requiring a more detailed sleep clinic review, which would further erode the business case for this treatment. Issue 6. Partner Utilities. SATA considers that in the context of this Technical Appraisal partners should be considered to have the same importance as carers. In many cases it is the patient's partner who first becomes aware that the patient is displaying symptoms of OSA, and it is very often the partner who persuades a reluctant patient to seek diagnosis and treatment. Where EDS remains present even after

	CPAP treatment is commenced, it is very likely to be the partner who observes sleepiness symptoms during the day. BP & HR – CS B.2.10.3.3. The CS reports small mean changes in BP and HR from baseline to week 12, but then argues that these changes are lower than changes reported by habitual coffee drinkers one hour after caffeine intake. SATA would simply observe that drinking coffee is a lifestyle choice, and any adverse effect on HR and BP can be moderated by drinking less coffee, switching to caffeine-free coffee or to tea, or giving up coffee altogether. Solriamfetol, on the other hand, would be a prescribed drug, with no option other than stopping taking it, in which case EDS would return. The comparison between coffee intake and Solriamfetol in terms of raised HR and BP may therefore be an oversimplification. The ERG review reported that the cost of established clinical management for OSA is excluded because adding Solriamfetol to standard OSA is expected to have no impact. SATA would argue that the issues, and the possibility of increased costs as a result, described in the previous paragraphs calls this assumption into question. The CS argues that there were minimal changes in use of primary OSA therapy during the TONES 3 and 4 trials. However, the possibility exists that compliance within the structured and closely monitored setting of a trial might be greater than compliance in real life treatment.

Patient population	
11. Are there any groups of patients who might benefit more or less from the technology than others? If so, please describe them and explain why.	The only patients who might benefit from the technology are those whose symptoms of EDS have not been controlled by CPAP. The CS does not address whether the technology might benefit any patients with mild OSA but who nevertheless display symptoms of EDS.
Equality	
12. Are there any potential equality issues that should be taken into account when considering this condition and the technology?	Many GPs, to the extent that they are fully aware of the condition, regard OSA as essentially a condition which affects middle aged and older, overweight, males. This view is accepted in the CS (B.1.3 – Overview of OSA). However it is increasingly being recognised that OSA affects younger males, women, and even children. The increasing levels of obesity in the UK population, including in children, are likely to increase the prevalence of OSA in both sexes and in all age groups. The CS does not reflect this.

Other issues	
13. Are there any other issues that you would like the committee to consider?	SATA would hope that if this technology is approved by NICE it would be on the basis that for patients with OSA and EDS (OSAS) there would be an expectation that sleep clinics would fully explore adjustment to standard CPAP treatment to control EDS before resorting to this technology.

Key messages

14. In up to 5 bullet points, please summarise the key messages of your submission:

- Minimal changes in use of primary OSA therapy during TONES 3 & 4 trials might be due to the more structured trial environment. Changes in use of primary OSA therapy may be rather greater in real life.
- Partners should be considered to have the same importance as carers.
- For several reasons the assumption that adding Solriamfetol to standard treatment will have no impact on established clinical management, and the exclusion of the cost of established clinical management as a result, is questionable.
- the CS may understate minimal changes to OSA therapy.
- OSA is no longer a condition which predominantly affects older overweight males.

Thank you for your time.

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

Solriamfetol for treating excessive daytime sleepiness caused by obstructive sleep apnoea

Produced by	Southampton Health Technology Assessments Centre (SHTAC)
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Declared competing interests of the authors and advisors

Dr O'Reilly has received reimbursement of an educational conference registration fee and travel costs from Jazz Pharmaceuticals for attendance at the British Sleep Society Conference in November 2019. This meeting was non-promotional and did not contain any reference to solriamfetol.

Rider on responsibility for report

The view 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.

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Contributions of authors

Irina Tikhonova critically appraised the health economic systematic review, critically appraised the economic evaluation, and drafted the report. Lorna Hazell critically appraised the clinical effectiveness evidence 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 evidence and drafted the report. Olu Onyimadu critically appraised the health economic systematic review, critically appraised the economic evaluation, and drafted the report. Jonathan Shepherd critically appraised the clinical effectiveness evidence, 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

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LIST OF ABBREVIATIONS

AE	Adverse event
AIC	Academic in confidence
AHI	Apnoea Hypopnoea Index
AQOL	Assessment of Quality of Life
BNF	British National Formulary
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
CS	Company submission
CSR	Clinical study report
DSU	Decision Support Unit
DVLA	Driving and Vehicle Licence Authority
EDS	Excessive daytime sleepiness
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
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

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
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 ERG notes that the decision problem matches the NICE scope on most parameters, with some minor discrepancies which we consider acceptable. We do not consider there to be any issues of uncertainty requiring further attention.

1.2 Summary of the key issues in the clinical effectiveness evidence

Issue 1 Potential reduction in patient compliance with primary OSA therapy during concomitant solriamfetol treatment

Report section	**3.2.6.1.4**
Description of issue and why the ERG has identified it as important	Compliance with primary OSA therapy may be compromised if patients perceive a reduction in sleepiness with solriamfetol and they prefer the simplicity of taking solriamfetol (a once daily tablet) rather than CPAP treatment or following lifestyle advice. If so, this could impact on other OSA symptoms and possibly limit the effectiveness of solriamfetol in reducing residual EDS. In an exploratory analysis, the CS reports that use of primary OSA therapy devices did not change in the short term (12 weeks, TONES 3 trial) or over the longer term (up to 1 year, TONES 5 trial). However, the ERG notes a number of limitations with this analysis including poor reporting of patient characteristics; substantial amount of missing electronic compliance data, and the potential limited generalisability of compliance in the clinical trial setting to real-world settings.
What alternative approach has the ERG suggested?	None at present
What is the expected effect on the cost-effectiveness estimates?	Currently unknown. This would be difficult to model, as additional data would be needed to explore the impact of different levels of compliance to primary OSA therapy on EDS and other OSA symptoms.
What additional evidence or analyses might help to resolve this key issue?	Greater clarity and transparency in the reporting of the exploratory compliance analysis: • Clarification of the relevant analysis populations in TONES 3 and TONES 5 for this outcome • Sensitivity analysis to assess the impact of missing data • Sub-group analysis stratified by compliance at baseline Supporting evidence may also be useful if available:

	• The likelihood of compliance issues over the longer term e.g. was this seen in users of modafinil in the real-world setting? • What effect a drop in CPAP compliance has on ESS (and other outcomes e.g. AHI, snoring, cardiovascular risk) Further expert advice on how compliance is measured and the likely impact if compromised. And how clinicians would react if CPAP compliance was seen to fall after initiation of solriamfetol.

1.3 Summary of the key issues in the cost effectiveness evidence

Issue 2 Model population

Report section	**4.2.3**
Description of issue and why the ERG has identified it as important	The mean baseline ESS ([redacted]) in the company's base case model is increased by the use of IPD for people with ESS>10 (rather than ESS≥10 as in the TONES 3 trial population). The company argues that ESS=10 falls within the range considered 'normal' in UK clinical practice (CS Table 6 and page 118). In addition to increasing the mean ESS at baseline for the modelled population, this assumption increases the estimated proportion of responders over the 12-week induction period (see Table 26 below). We believe that for the main analysis, the definition of EDS from the European Medicines Agency and consistent with the TONES 3 trial (i.e. ESS ≥10) would be more appropriate. Restriction to a population with ESS>10 is likely to enhance the effectiveness, and hence cost-effectiveness of solriamfetol. However, this increases uncertainty by reducing the sample size on which the analysis is based.
What alternative approach has the ERG suggested?	We use the whole TONES 3 population (ESS ≥10) in the ERG base case. We test the effect of restricting the population to people with ESS>10 (as in the company base case) and ESS>12 in scenario analyses.
What is the expected effect on the cost-effectiveness estimates?	The company's base case ICER increases from £34,121 to £36,118 per QALY with the ESS ≥10 population. Increasing the baseline ESS threshold for the population to ESS>12 reduces the base case ICER to £29,024 per QALY.
What additional evidence or analyses might help to resolve this key issue?	Expert opinion on the ESS level that best reflects a 'normal' level of daytime sleepiness, and the group of patients who would most benefit from solriamfetol treatment.

Issue 3 Definition of treatment response

Report section	4.2.6.3
Description of issue and why the ERG has identified it as important	There is considerable variation in the definition of treatment response in clinical practice, including a reduction of ESS scores of 2 to 3 points, and normalisation of EDS (i.e. reduction in ESS score below 10, as defined in the European Marketing Authorisation for solriamfetol). Clinical advice to the ERG is that clinicians would also consider other factors when assessing treatment effectiveness. In the company's base case, response is defined as at least a 3-point reduction in ESS from baseline to 12 weeks. Alternative definitions of response as reduction in ESS of 2 or 4 or more points are assessed in scenario analyses. The definition of response is important, because it would be used to assess the effectiveness of solriamfetol induction treatment in clinical practice. The economic model assumes that treatment would be discontinued at 12 weeks if the response was inadequate. A less stringent definition of response is likely to reduce the average effectiveness and cost-effectiveness of continued treatment.
What alternative approach has the ERG suggested?	The ERG's base case includes a response definition of an ESS reduction of 2 or more points, with scenario analyses of ESS reductions of 3 or more and 4 or more points. This is intended to reflect differences in response assessment in clinical practice.
What is the expected effect on the cost-effectiveness estimates?	With a response definition of an ESS reduction of 2 or more points, there is a small increase in the company's base case ICER. A definition of 4 or more points reduces the company's base case ICER to £32,500 per QALY.
What additional evidence or analyses might help to resolve this key issue?	Clinical advice on the appropriate definition of treatment response, in terms of ESS reduction or other measurable factors.

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

Report section	4.2.6.2
Description of issue and why the ERG has identified it as important	In the TONES 3 trial, reductions in mean ESS scores were observed for patients in both solriamfetol and placebo arms. The company use a 'centring' approach to adjust TONES 3 individual patient data (IPD) used in the economic model by removing the placebo arm effect from both study arms. This is appropriate if the placebo arm improvement was caused by observation of patients in the clinical trial that would not have occurred in routine practice (a 'Hawthorne' effect). However, it would not be appropriate if the placebo effect was caused by a natural 'regression to the mean', as this would still have occurred outside the clinical trial.

	The company provides a good discussion of potential causes for the ESS placebo effect in support of their centring approach (CS B.3.3.2). In particular, we note their argument that a placebo effect was not observed in TONES 3 for the Maintenance of Wakefulness Test (MWT), which tends to support the argument that the ESS placebo effect was not caused by regression to the mean. We note, however, that the MWT and ESS do measure different (though related) things, and it is possible that MWT is more stable over time, mitigating against a regression to the mean effect, whereas the ESS as a self-reported measure is more susceptible to natural variation, and hence to regression to the mean. There is no direct evidence for the cause of the ESS placebo effect or the appropriateness of adjustment to remove it from the economic analysis.
What alternative approach has the ERG suggested?	We adapted the company's model to use uncentred ESS scores (unadjusted IPD). This allows us to compare cost-effectiveness with and without the company's centring approach. Given the lack of direct evidence to support centring, we use the uncentred approach in ERG analysis, but present results with centred ESS in scenario analysis.
What is the expected effect on the cost-effectiveness estimates?	Centring of the IPD is the most influential model assumption. Removal of centring increases the company's base case ICER by over £100,000 per QALY gained.
What additional evidence or analyses might help to resolve this key issue?	Observational evidence on the degree of natural variation in ESS over time for people with EDS caused by OSA that has not been satisfactorily treated with established clinical management. Expert advice on how ESS is seen to vary over time in patients from this population from the initial consultation, without solriamfetol treatment.

Issue 5 Health utility values

Report section	**4.2.7**
Description of issue and why the ERG has identified it as important	EQ-5D-5L results from the TONES 3 trial did not show consistent trends over time or evidence of treatment effects for solriamfetol. The company argue that this is due to the high baseline EQ-5D utilities in the TONES 3 population and question the sensitivity of the EQ-5D for detecting the Health-Related Quality of Life (HRQoL) effects of OSA. The other generic HRQoL measure in the trial (the SF-36) did show some evidence of a treatment effect for solriamfetol, although this was inconsistent between doses. There is some evidence from the literature that utility measures that include an energy or vitality dimension, such as the SF-6D or AQOL, are better at predicting overall HRQoL. However, we note that the company has not presented SF-6D results for TONES 3.

	The company use a 'mapping' approach to estimate EQ-5D utility as a function of ESS in their base case economic analysis. A new mapping equation was estimated from data collected from an online sample of people with self-reported OSA. The NHWS mapping study was described in detail and it appeared to be well-conducted. Other sources of utility estimates used in the model are the ESS to EQ-5D mapping study by McDaid et al. that was used in the NICE appraisal of CPAP for OSA (TA139); and a new time trade off (TTO) study.
What alternative approach has the ERG suggested?	On balance, we agree with the company's use of the NHWS mapping formula in the base case, and the McDaid formula in a scenario. We do not favour use of the TTO utility estimates, as these place a very high emphasis on daytime sleepiness in the health state descriptions and so are unlikely to be comparable with utility values in other NICE appraisals derived from the EQ-5D.
What is the expected effect on the cost-effectiveness estimates?	The ICER with the McDaid mapping formula was very similar to the company's base case result (with NHWS mapping). The TTO patient utility scenario was a more favourable, yielding an ICER well below £20,000 per QALY gained. Cost-effectiveness estimates based on TONES 3 trial utilities are not available but would yield a very high ICER or solriamfetol would be dominated.
What additional evidence or analyses might help to resolve this key issue?	SF-6D results for TONES 3 would help to clarify the direct utility effect of solriamfetol add-on therapy. Clarification of whether the valuation method used to calculate index scores for the EQ-5D-5L in TONES 3 and in the NHWS mapping study are consistent with the NICE Reference Case.

Issue 6 Partner utilities

Report section	**4.2.7.4**
Description of issue and why the ERG has identified it as important	The NICE reference case specifies that economic evaluations should include "all direct health effects, whether for patients or, when relevant, carers". Partners of people with OSA are not necessarily carers, although some would be. However, paragraph 5.1.7 of the NICE methods guide states that the perspective on outcomes should include "all direct health effects, whether for patients or for other people". It is therefore unclear whether partner utilities should be included in the assessment of cost-effectiveness. The company TTO study estimated utility associated with health states describing OSA and four levels of EDS severity from the perspective of patients and of their partners. The study was described in detail and appeared to have followed recommended methods. However, the ERG questions whether the TTO utility estimates are comparable with utilities obtained from the EQ-5D, which NICE prefers. The TTO data were analysed to derive a simple formula to predict partner utility as a function of patient utility. The company used this for

	scenario analysis, by applying it to NHWS, McDaid and TTO patient utility estimates. Although not dependent on the absolute TTO utilities, we question the robustness of this formula.
What alternative approach has the ERG suggested?	We do not include partner utilities in the ERG base case analysis. We have concerns over both the principle of whether partner utilities should be included, and the indirect estimation from TTO data.
What is the expected effect on the cost-effectiveness estimates?	Inclusion of partner utilities, as estimated with the TTO partner-patient utility function increases the estimated QALY gain, and hence reduces ICERs with all methods of patient utility estimation.
What additional evidence or analyses might help to resolve this key issue?	Clarification of precedent for NICE appraisals on the inclusion of partner utilities in health economic evaluations. Evidence of the magnitude of utility loss associated with living with a partner who has OSA and EDS, derived according to NICE Reference Case methods.

Issue 7 Treatment discontinuation and loss of response rates

Report section	**4.2.6.4**
Description of issue and why the ERG has identified it as important	The company report that solriamfetol treatment discontinuation due to treatment emergent adverse events (TEAEs) and loss of response in the TONES 3 and 5 trials was dose dependent. However, the modelled rates in the company base case are the same across all solriamfetol doses. Loss of response with standard care is not an issue for the company model, with 'centring' assumptions, because ESS is assumed to be constant without solriamfetol. However, in our version of the model, we assume that ESS can vary with standard care and hence response is possible without solriamfetol. The subsequent change in ESS and loss of response over time with standard care is highly uncertain because we do not have follow up beyond 12 weeks.
What alternative approach has the ERG suggested?	For the ERG base case, we apply dose-dependent discontinuation rates due to TEAEs and loss of response with solriamfetol treatment, estimated from TONES 5. For the ERG standard care arm, we assume a loss of response rate based on the weighted average of discontinuation due to loss of efficacy from the solriamfetol treatment arms.
What is the expected effect on the cost-effectiveness estimates?	The impact of introducing dose-dependent discontinuation rates in the company's base case model depends on the dose-split assumption: see below. Without the assumption of a loss of response rate in the standard care arm, the ERG non-centred model predicts a higher ICER. However, we consider this to be unrealistic.

What additional evidence or analyses might help to resolve this key issue?	Observational data on how ESS changes over time with standard care, as suggested above to investigate the placebo effect and appropriateness of centring, would also help to address the question of the loss of response rate with standard care.

Issue 8 The impact of adverse events

Report section	**4.2.8.3.2**
Description of issue and why the ERG has identified it as important	The company model does not include any disutility or treatment cost for TEAEs that did not lead to discontinuation. This was based on the observation that most AEs in TONES 3 were transient and mild/moderate in severity. For adverse events that led to treatment discontinuation, the company model assumes the cost of one general practitioner contact. We note that a proportion of serious adverse events (SAEs) in the 150 mg arm of TONES 5 led to hospitalisation [redacted].
What alternative approach has the ERG suggested?	We included a cost for SAEs that led to hospitalisation in the ERG base case.
What is the expected effect on the cost-effectiveness estimates?	Including the estimated cost of hospitalisation due to SAEs increased the company's base case ICER to £35,079 per QALY gained.
What additional evidence or analyses might help to resolve this key issue?	None

Issue 9 Solriamfetol dose split

Report section	**4.2.8.1.2**
Description of issue and why the ERG has identified it as important	The proportion of people taking the 37.5 mg, 75 mg and 150 mg doses of solriamfetol in clinical practice is uncertain. This obviously impacts on the estimated cost of solriamfetol, but it also affects the overall estimates of response and ESS change, and the rates of discontinuation. The company states that "US data suggests a [redacted] dose split for the 37.5 mg, 75 mg and 150 mg doses, respectively" (CS page 169). But they suggest that UK prescribers will be more conservative compared with those in the US and assume a split of 40/40/20 in the company base case. This may be a reasonable assumption, although we note that one of our clinical advisors has suggested that some clinicians may want to start patients on the 75 mg dose to reduce the time and resource needed for dose titration. The company argue that the dose

	split in the TONES 5 open label follow up study is not informative for clinical practice, because participating clinicians were advised to increase to the maximum dose subject to tolerance.
What alternative approach has the ERG suggested?	We adopt the dose split of [redacted] based on US data in our base case analysis, with scenarios for 40/40/20 and 20/40/40.
What is the expected effect on the cost-effectiveness estimates?	Scenarios with more patients on higher doses of solriamfetol (dose splits of 20/40/40 and [redacted]) both increased the company's base case ICER.
What additional evidence or analyses might help to resolve this key issue?	Additional utilisation data from other countries with similar prescribing behaviour may help to inform the estimated use of solriamfetol 37.5 mg, 75 mg and 150 mg doses in the UK.

1.4 Summary of the ERG's preferred assumptions and resulting ICER

The ERG's preferred assumptions include the following changes to the company's base-case assumptions:

1. The use of uncentred IPD from the TONES 3 mITT population to estimate treatment effect and proportion of responders (section 4.2.6.2)
2. Amending the model by adding a new health state for patients who discontinue solriamfetol due to AEs but are still considered responders (section 6.1)
3. Using discontinuation rates due to loss of response and SAEs stratified by treatment dose from TONES 5 (section 4.2.6.4)
4. Patient population as in TONES 3, with ESS ≥ 10 (section 4.2.3.1)
5. Defining treatment response as a reduction in ESS from baseline of at least 2 points (section 4.2.6.3)
6. The proportion of patients receiving 37.5 mg, 75 mg and 150 mg doses of solriamfetol [redacted] (section 4.2.8.1.2)
7. Including the cost of hospitalisation due to serious AEs in patients treated with solriamfetol (section 4.2.8.3.2)

Table 1 ICER resulting from ERG's preferred assumptions (base case)

	Total Costs	Total QALYs	Change in costs	Change in QALYs	ICER £/QALY
Standard care	£0	10.864	£0	0.000	£0
Standard care with solriamfetol	£19,623	10.983	£19,623	0.119	£165,376

1.5 Summary of exploratory and sensitivity analyses undertaken by the ERG

Table 2 Exploratory scenario analyses undertaken by the ERG

Individual scenarios on the base case	Treatment	Costs	QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
ERG base case	SC	£0	10.864	£0	0.000	£0
	SOL	£19,623	10.983	£19,623	0.119	£165,376
ESS>10 at baseline (company base case)	SC	£0	10.831	£0	0.000	£0
	SOL	£19,414	10.936	£19,414	0.104	£186,063
ESS>12 at baseline	SC	£0	10.746	£0	0.000	£0
	SOL	£19,892	10.883	£19,892	0.137	£146,596
Centring	SC	£0	10.417	£0	0.000	£0
	SOL	£13,112	10.722	£13,112	0.306	£42,877
Timepoint of response assessment: 8 weeks	SC	£0	10.865	£0	0.000	£0
	SOL	£19,604	10.983	£19,604	0.119	£165,231
Time to treatment response: 2 weeks	SC	£0	10.864	£0	0.000	£0
	SOL	£19,623	10.983	£19,623	0.119	£165,376
Discontinuation rates: company base case for LoE and TEAEs	SC	£0	10.870	£0	0.000	£0
	SOL	£14,772	10.917	£14,772	0.047	£315,667
Treatment response: reduction in ESS≥3	SC	£0	10.762	£0	0.000	£0
	SOL	£18,299	10.932	£18,299	0.170	£107,486
Treatment response: reduction in ESS≥4	SC	£0	10.724	£0	0.000	£0
	SOL	£16,558	10.886	£16,558	0.162	£102,051
Cost of hospitalisation due to SAEs	SC	£0	10.864	£0	0.000	£0
	SOL	£19,044	10.983	£19,044	0.119	£160,490
40/40/20 SOL dose split (company base case)	SC	£0	10.856	£0	0.000	£0
	SOL	£17,325	10.963	£17,325	0.107	£161,903
20/40/40 SOL dose split	SC	£0	10.891	£0	0.000	£0
	SOL	£23,643	11.048	£23,643	0.157	£150,753
Time horizon: 1 year	SC	£0	0.315	£0	0.000	£0
	SOL	£964	0.321	£964	0.005	£183,593
Time horizon: 5 years	SC	£0	2.597	£0	0.000	£0
	SOL	£6,591	2.634	£6,591	0.038	£175,466
Time horizon: 50 years	SC	£0	10.866	£0	0.000	£0
	SOL	£19,624	10.985	£19,624	0.119	£165,364
Compliant patients	SC	£0	10.911	£0	0.000	£0
	SOL	£19,201	11.017	£19,201	0.105	£182,476
Non-compliant patients	SC	£0	11.140	£0	0.000	£0
	SOL	£21,105	11.298	£21,105	0.158	£133,718
ICER for 50%/50% split (compliant/non-compliant)	SC	£0	11.026	£0	0.000	£0
	SOL	£20,153	11.157	£20,153	0.132	£153,222

SC: Standard Care; SOL: Solriamfetol combination.

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 obstructive sleep apnoea. 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 10th June 2020. A response from the company via NICE was received by the ERG on 24th June 2020 and this can be seen in the NICE committee papers for this appraisal.

2.2 Background

2.2.1 Background information on obstructive sleep apnoea (OSA) and OSA with excessive daytime sleepiness (EDS)

The CS provides an overview of obstructive sleep apnoea (OSA) (CS section B.1.3) describing its aetiology, risk factors (e.g. obesity, male sex, older age), night-time clinical symptoms (e.g. loud snoring), daytime clinical symptoms (e.g. sleepiness, lack of energy), diagnosis and severity measurement and its long-term consequences and complications (e.g. cardiovascular disease).

OSA is described as a common long-term sleep disorder, characterised by the repeated occurrence of complete (apnoea) or partial (hypopnoea) closures of the upper airway during sleep. Commonly, people may awaken one or more times during the night and then fall back to sleep. They may wake up in the morning feeling tired, but not necessarily be aware of their night-time awakenings and that they may have OSA.

The severity of OSA is measured using the Apnoea Hypopnoea Index (AHI)) and is one of the factors determining type of **primary OSA therapy** given:

- **Mild OSA** may be managed effectively in many patients with lifestyle changes such as improved sleep hygiene and weight loss, smoking cessation and alcohol avoidance. Oral appliance therapies, such as mandibular appliances (which positions the jaw slightly forward tightening the upper airway to prevent obstruction of the airway during sleep) might also be used to reduce symptoms such as snoring.

- **Moderate to severe OSA** requires additional interventions, the most widely used of which in the UK is positive airway pressure (PAP) / continuous positive airway pressure (CPAP).
- NICE guidance TA139 (2008) recommends CPAP for adults with moderate or severe symptomatic obstructive sleep apnoea hypopnoea syndrome (OSAHS), or as a treatment option for adults with mild OSA if their symptoms adversely affect their quality of life and daily activities.
- **Severe OSA** cases may require surgery to resect the uvula and redundant retrolingual soft tissue. However, rates of surgery are generally low.
- Oral appliance therapy remains an option across all severities of OSA, e.g. for those who do not tolerate CPAP.

Excessive daytime sleepiness (EDS) is a prominent symptom of OSA. People with EDS experience periods of sleepiness during the day of varying extremity, which can trigger low mood, anxiety and impaired cognitive function, amongst other things. However, not everyone with OSA will experience EDS, and likewise, not everyone with EDS will have OSA (EDS can be caused by other factors, including central nervous system disorders, or shift work).

The CS notes that optimal management of OSA can reduce symptoms related to the condition itself (e.g. apnoeic/hypopnoeic episodes), as well as EDS (e.g. dozing during the day). However, for a small proportion of patients EDS persists despite optimal therapy, a phenomenon referred to as **residual EDS**.

The proportion of OSA patients who experience residual EDS is unknown. The CS cites studies which estimate that 6%–22% of patients who are compliant with CPAP will report residual EDS that cannot be explained by any other cause. Expert clinical opinion to the ERG suggests between 10%- 20% of patients receiving optimal OSA therapy will have residual EDS.

Residual EDS can negatively affect a person's health-related quality of life (HRQoL). However, some patients may self-report 'normal' (HRQoL). The cause of this is unknown, but may suggest that some patients have adapted to their EDS.

The CS states that the severity of EDS is independent of the severity of OSA and therefore "EDS must be managed independently of the underlying OSA" (CS page 15). However, the ERG's understanding, informed by expert clinical opinion and the literature, is that primary

OSA therapy can alleviate EDS symptoms (NB. EDS as measured by the Epworth Sleepiness Scale was the key clinical effectiveness outcome measure that informed the analysis underpinning NICE's recommendation of CPAP for OSAHS – NICE TA139). Discordance between OSA severity (i.e. AHI scores) and EDS severity can occur in patients with OSA and EDS, including those patients who are benefitting from optimal primary OSA therapy but who experience residual EDS. It is the subgroup of patients whose EDS is not satisfactorily managed by a primary OSA therapy who require treatment to reduce sleepiness and improve wakefulness (the ability to remain awake and alert)

2.2.2 Background information on solriamfetol

The intervention under appraisal is solriamfetol (Sunosi ®). The CS describes solriamfetol as a centrally acting sympathomimetic agent (i.e. one which promotes the stimulation of sympathetic nerves)), intended to reduce sleepiness and improve wakefulness in people with EDS (CS section B.1.2). The mechanism(s) by which solriamfetol promotes wakefulness are not yet fully characterised but is/are thought to be through activity as a dopamine and noradrenaline reuptake inhibitor.

Solriamfetol received its marketing authorisation in Europe by the European Commission on 16th January 2020. The marketing authorisation covers two separate treatment indications:

- Improve wakefulness and reduce EDS in adult patients with OSA whose EDS has not been satisfactorily treated by primary OSA therapy, such as continuous positive airway pressure (CPAP).
- Improve wakefulness and reduce EDS in adult patients with narcolepsy (with or without cataplexy).

The scope of this current appraisal, and therefore the CS, covers the first indication only. The second indication, for the treatment of EDS in patients with narcolepsy, is the subject of a separate concurrent NICE technology appraisal (ID1602).

Solriamfetol is orally administered once daily, and is available in doses of 37.5 mg, 75 mg, and 150 mg. The recommended starting dose is 37.5 mg for patients with OSA which can be titrated at intervals of at least three days up to a maximum dose of 150 mg. A 300 mg dose was included in the solriamfetol clinical trial programme but was not licensed for use in Europe.

2.2.3 The current treatment pathway for EDS in OSA, and the proposed place of solriamfetol

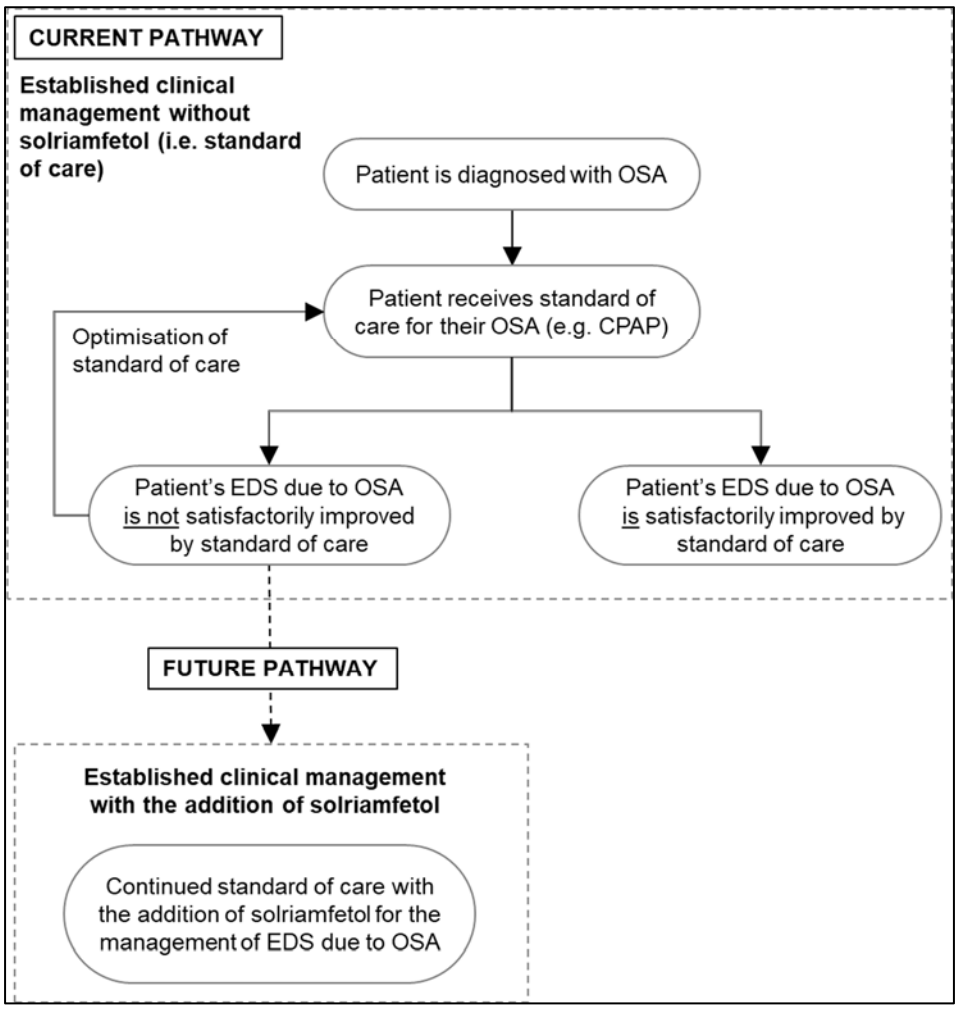


Figure 1 The company's proposed positioning of solriamfetol in the OSA treatment pathway

Source: CS Figure 1.

Figure 1 illustrates the company's proposed place of solriamfetol in the care pathway for OSA. Solriamfetol is intended to be prescribed in addition to optimal primary OSA therapy (e.g. CPAP). The ERG's clinical experts note that compliance to primary OSA therapy varies between patients, and that they would expect patients to demonstrate good compliance to be considered for solriamfetol treatment.

The CS notes that, with the exception of solriamfetol, no other licensed therapies are indicated to treat residual EDS in OSA. Expert clinical opinion to the ERG mostly agrees with the company's description of current management of EDS due to OSA. However, they

commented that drug therapies such as dexamfetamine and modafinil are sometimes used off-label to treat residual EDS in OSA.

Modafinil's indication as a treatment for residual EDS in OSA was removed by the European Medicines Agency (EMA) in 2010 after their review of safety concluded its benefits do not outweigh its risks. This review has since been criticised for only including efficacy data from two clinical trials submitted to support modafinil's marketing authorisation. A subsequent independent systematic review and meta-analysis[1] included 10 randomised placebo-controlled trials of modafinil for the treatment of residual EDS in OSA (a total of 1466 patients), and reported a more favourable risk-benefit profile, recommending that clinicians consider this, rather than the EMA review, in their prescribing decisions.

Expert advice to the ERG is that, anecdotally, this systematic review has influenced the off-label use of modafinil to treat residual EDS. One expert suggests that 5%-10% of patients (of the 10-20% of patients with residual EDS on optimised primary OSA therapy) will be managed by a sleep specialist comfortable to use modafinil off label. The majority of patients are managed by general respiratory physicians, and it is unlikely that they would prescribe modafinil. That modafinil is used in a minority of patients indicates that cannot be considered as standard NHS practice and thus potentially an eligible comparator to solriamfetol in the decision problem for this appraisal. However, further clinical input would be welcome to confirm this.

Finally, the ERG notes that a separate NICE technology appraisal of pitolisant, with or without primary OSA therapy, is running concurrently to this appraisal (ID1065). The scope of the pitolisant appraisal is very similar to the scope of this appraisal of solriamfetol. If pitolisant and solriamfetol were both recommended for the treatment of EDS by NICE they would be potential comparators in any future NICE appraisal of interventions to treat EDS in OSA.

ERG conclusion on the company's background information

The CS provides a detailed description of the characteristics of EDS in OSA. The CS provides an adequate justification for the place of solriamfetol as a treatment for residual EDS patients with OSA whose EDS has not been satisfactorily treated by primary OSA therapy. The company's description of the treatment pathway mostly concurs with expert clinical opinion to the ERG, though additionally our experts noted that stimulant drugs and modafinil are used off-label in some patients with residual EDS. Due to safety concerns modafinil would be prescribed by more experienced

sleep physicians, rather than general respiratory physicians, the latter who manage the majority of OSA cases.

2.3 Critique of the company's definition of the decision problem

Table 3 summarises the company's decision problem specified in relation to the final NICE scope. The ERG notes that the decision problem matches the NICE scope on most parameters, with some minor discrepancies which we consider acceptable. As mentioned in the previous section, expert clinical opinion to the ERG is that some centres treat patients with residual EDS with drugs such as modafinil, used off-label. The ERG notes that these can potentially be included as comparators in NICE appraisals if they are known to be standard practice. However, it appears that such drugs are prescribed in only a minority of patients and therefore cannot be considered standard practice.

Table 3 Summary of the decision problem

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope	ERG comments
Population	Adults with OSA whose EDS has not been satisfactorily treated by primary OSA therapy, such as CPAP.	Adults with OSA whose EDS has not been satisfactorily treated by primary OSA therapy, such as CPAP.	N/A	Decision problem matches the NICE scope
Intervention	Solriamfetol with or without primary OSA therapy	Solriamfetol with or without primary OSA therapy	N/A	Decision problem matches the NICE scope (NB. The economic analysis assumes only solriamfetol *with* primary OSA therapy).
Comparators	Established clinical management without solriamfetol	Established clinical management without solriamfetol (i.e. standard of care without solriamfetol)	N/A	The NICE scope does not explicitly define established clinical management, but it does summarise

				commonly used interventions. The CS uses the term 'standard of care without solriamfetol' synonymously with established clinical management. The CS and the NICE scope describe similar interventions that comprise standard of care (e.g. lifestyle changes, CPAP, oral devices) However, neither the scope nor the decision problem mentions off-label use of drugs for residual EDS in OSA.
Outcomes	• EDS • Fatigue • Length of life • Adverse effects of treatment • Health-related quality of life	• EDS • Adverse effects of treatment • Health-related quality of life	Decision problem omits fatigue and length of life. CS states: • Fatigue - not an outcome measure used to determine response to OSA therapy and not included in the TONES trials. • Length of life - no effects of solriamfetol on mortality are anticipated but the CS	The ERG agrees with the company's rationale, based on our experts' clinical opinion.

			does model length of life.	
Economic analysis	NICE reference case	NICE reference case	N/A	Decision problem matches the NICE scope
Subgroups	Where data allow: • Mild, moderate and severe OSA • People who cannot have or have refused CPAP • People not continuing primary OSA therapy, such as CPAP	The decision problem does not specify the presence or absence of any sub-groups.	The CS does not comment on whether the subgroups in the NICE scope were considered for inclusion in the decision problem. However, the CS does report subgroup analyses according to compliance to primary OSA therapy (at randomisation in TONES 3). The CS also reports change in frequency of primary OSA therapy (TONES 3 exploratory outcome)	The ERG notes that compliance to primary OSA therapy was a pre-specified subgroup analysis in TONES 3, and it is a clinically relevant factor in the optimal management of OSA and EDS. The ERG notes that this subgroup may include some patients who cannot tolerate or refuse CPAP. Subgroup analysis by severity of OSA may be less relevant for this appraisal as severity of EDS symptoms is independent of OSA.
Special considerations	• None stated	Not specifically referred to in the decision problem	N/A	No comment

Source: NICE scope and CS Table 1
N/A = Not applicable

3 CLINICAL EFFECTIVENESS

3.1 Critique of the methods of review(s)

The CS reports that a clinical systematic literature review was not conducted for this appraisal (B.2.1). The justification for this is because solriamfetol clinical effectiveness at the current time is available only from the company's sponsored solriamfetol clinical trial programme. Literature searching would therefore be highly unlikely to identify any other relevant studies.

The ERG notes that literature searching would, however, be necessary to identify clinical effectiveness evidence for comparator treatments, for example, to inform an indirect treatment comparison. The company's pivotal TONES 3 phase III RCT permitted the use of primary OSA therapy in the solriamfetol and placebo arms, thus providing the head-to-head comparison specified in the decision problem and obviating the need for an indirect comparison. On this basis the ERG concurs with the company's decision not to conduct a systematic review of clinical effectiveness.

3.2 Critique of studies of the technology of interest, the company's analysis and interpretation

3.2.1 Included studies

As noted above, the company did not conduct a systematic review to identify studies reporting the clinical effectiveness of solriamfetol for the treatment of OSA. Instead, the CS lists the four trials from the company's phase III solriamfetol clinical trial programme ('Treatment of Obstructive sleep apnoea and Narcolepsy Excessive Sleepiness – TONES') (section B.2.2 of the CS).

The relevant evidence for solriamfetol for treating EDS in OSA comes from three trials, all of which are complete and published in peer-reviewed journals: TONES 3,[2] TONES 4,[3] and TONES 5.[4]) The ERG believes that all relevant clinical effectiveness studies of solriamfetol in OSA have been included.

3.2.1.1 Trial characteristics

TONES 3 is the pivotal phase III RCT in patients with EDS due to OSA, which supported the company's EMA licence application. Patients were randomised to 12 weeks of solriamfetol (four solriamfetol arms 37.5 mg 75 mg, 150 mg and unlicensed 300 mg doses once daily) or placebo. Patients randomised to the 150 mg and 300 mg solriamfetol doses received 75 mg and 150 mg doses respectively for the first three days and their full dose from day 4. The primary efficacy outcomes were the change from baseline in Epworth sleepiness scale (ESS) and the Maintenance of wakefulness test (MWT) at week 12.

TONES 4 was also a phase III RCT in which all patients were first titrated to and stabilised on their maximum tolerated solriamfetol dose (75 mg, 150 mg or unlicensed 300 mg) before a randomised 2-week withdrawal to placebo or to continued solriamfetol took place. The primary outcomes in TONES 4 were the change in baseline ESS and MWT from the beginning to the end of the withdrawal phase.

TONES 5 was an open-label study of the safety and tolerability of solriamfetol (75, 150 or 300 mg) for up to 52 weeks. During the open-label study there was a 2-week randomised withdrawal component for some participants after a minimum of 26 weeks open-label treatment. The primary outcome for the randomised withdrawal phase of TONES 5 was the change in baseline ESS from the beginning to the end of the withdrawal phase.

The ERG's full review of the efficacy, safety and HRQoL outcome measures used in the three TONES trials is provided in section 3.2.4 of this report. The CS reports on final data cuts for all three studies.

The 300 mg solriamfetol dose was not included in the licence, thus data from the 300 mg arm of TONES 3 are not presented in the CS. In the randomised withdrawal RCT TONES 4 and the randomised withdrawal component of TONES 5, patients who remained on solriamfetol are treated as a single combined solriamfetol group, regardless of the solriamfetol dose they were receiving. The combined solriamfetol group, which includes patients on the 300 mg dose, was then compared to the patients randomised to placebo during the randomised withdrawal component of these trials.

The long-term TONES 5 study enrolled patients who had completed solriamfetol trials in OSA as well as patients who had completed solriamfetol trials in narcolepsy. Eligible participants from TONES 3 had no break in treatment before enrolling in TONES 5 (Group

A) and the duration of the open label phase for these participants was 40 weeks. Eligible participants from TONES 4 may have had a break in solriamfetol treatment before enrolling in TONES 5 (Group B) so the duration of treatment in the open-label phase was 52 weeks. The study designs of the three trials are shown in diagrammatic form in CS Figures 2, 3 and 4.

Eligibility criteria for the TONES 3, TONES 4 and TONES 5 studies are summarised in CS Table 4 (with additional detail in CS Appendix L.1 Tables 47 to 49). Patients with significant cardiovascular disease were excluded from the studies and patients were not permitted to use over the counter or prescription medications that could affect the evaluation of excessive sleepiness during the study. The ERG also notes that the dose titration schedules used in the TONES trials may be more rapid than could be achieved in typical NHS clinical practice.

Table 4 Characteristics of the three TONES trials

Characteristic	**TONES 3 (Study 14-003)**	**TONES 4 (Study 14-004)**	**TONES 5 (Study 14-005)**
Study design	Phase III multicentre, randomised, double-blind, placebo-controlled, five-arm parallel-group	Phase III multicentre, randomised-withdrawal, double-blind, placebo-controlled, two-arm parallel-group	Phase III open-label extension study including a 2-week randomised withdrawal phase for a subgroup of the enrolled population after completion of ≥6 months of solriamfetol treatment
Population	Adults (18-75 years) with OSA[a] and EDS (ESS score ≥10 and mean sleep latency <30 minutes[b]).	Adults (18-75 years) with OSA[a] and EDS (ESS score ≥10 and mean sleep latency <30 minutes)[b]	Adult patients who had previously completed solriamfetol clinical trials in OSA or narcolepsy indications (including TONES 3 and TONES 4).
Intervention	Solriamfetol 37.5 mg, 75 mg, 150 mg or unlicensed 300 mg once daily for 12 weeks	Solriamfetol 75 mg initiated and then titrated up or down to a maximum tolerated dose (75 mg, 150 mg or unlicensed 300 mg) (2 weeks), followed by a stable dose phase (solriamfetol	Solriamfetol (combined dose arm: 75, 150 or unlicensed 300 mg once daily); patients were up-titrated every three days starting at 75 mg to a maximum tolerated dose

Characteristic	TONES 3 (Study 14-003)	TONES 4 (Study 14-004)	TONES 5 (Study 14-005)	
		continued at stable dose for 2 weeks). Then randomised withdrawal to solriamfetol (75 mg, 150 mg or 300 mg) or placebo (2 weeks)	(300 mg unlicensed). Down-titration was permitted at any time for safety reasons. A maintenance phase followed for 40-52 weeks during which up to 3 dose adjustments were allowed within the first 12 weeks.	
Comparator	Placebo, once daily	Placebo, once daily (withdrawal phase)	**Open-label phase (40-52 weeks)**	**2-week withdrawal phase**
			None	Placebo, once daily
Number randomised	476	124	643 treated (417 with OSA)	282 (203 with OSA)
Randomisation ratio	1:1:2:2:2 [c]	1:1	Not applicable	1:1
Number completed	404	122	458 (308 with OSA)	278 ([redacted])
Number of centres	59 (US, Canada, France, Germany & the Netherlands)	34 (US, Finland France, Germany and Sweden)	79 (North America & Europe)	
Number of UK centres	Nil	Nil	Nil	

Characteristic	TONES 3 (Study 14-003)	TONES 4 (Study 14-004)	TONES 5 (Study 14-005)	
Primary Outcome(s)	Change from baseline ESS and MWT at week 12	Change from baseline ESS and MWT from the end of the stable-dose phase (week 4) to the end of the withdrawal phase (week 6)	Not applicable	Change in ESS from beginning to end of 2-week withdrawal phase
Sub-groups	[redacted]	[redacted]	[redacted]	

Source: This table was compiled by the ERG from information presented in the CS (Sections B.2.2, B.2.3, B.2.4.3.2 and Appendix D.1) and Schweitzer et al.[2]
Abbreviations: EDS - Excessive daytime sleepiness; ESS - Epworth sleepiness scale; MWT - Maintenance of Wakefulness Test; OSA - obstructive sleep apnoea
[a] diagnosed according to the ICSD-3 criteria and with current or prior use of a primary OSA therapy
[b] based on the mean of the first four trials of a 40-minute MWT
[c] randomisation ratio 1:1:2:2:2 to Solriamfetol 37.5 mg, 75 mg, 150 mg or 300 mg and the placebo groups respectively.

3.2.2 Patients' baseline characteristics

Patients' baseline characteristics in TONES 3 and TONES 4 (CS Section B.2.3.2 Tables 7 and 9) were similar. Participants from these trials formed the majority of the subgroup of participants with OSA in TONES 5 ([redacted]) and the baseline characteristics of participants in TONES 5 (CS Table 8) reflects this. An overview of baseline characteristics in TONES 3 and TONES 4 is provided in Table 5. The trial populations are aligned with the company decision problem in that they represent adult patients with OSA whose EDS has not been satisfactorily treated by primary OSA therapy. Approximately 70% of participants in these trials were compliant with primary therapy (defined as prior effective surgical intervention or PAP use ≥ 4 hours/night on ≥ 70% of nights or oral appliance use on ≥ 70% of nights) and the remaining approximately 30% were either using a device at a level lower than that specified for compliance, using no device at all or in whom a prior surgical intervention was deemed no longer effective (and with no compliant device use). The clinical experts the ERG consulted thought the trial populations had a higher ESS score at baseline in comparison to the population of people in the UK whose EDS has not been satisfactorily treated by primary OSA therapy, and that the level of primary therapy compliance was higher that is seen in routine clinical practice, but otherwise the populations were similar.

Table 5 ERG review of selected baseline characteristics of participants in the TONES 3 and TONES 4 trials

Baseline Characteristic	ERG Comment
Age	The mean age of trial participants (52 to 57 years across all trial arms).
Sex	A higher proportion of patients were male (approximately 62%). Prevalence of OSA is known to be higher in men.[5 6]
Ethnicity	Just over three quarters of the participants in the trials were white which is slightly lower than the general UK population.[7]
Body Mass Index (BMI)	Mean BMI in both trials was approximately 33 kg/m^2, this puts the average trial participant in an obese category by BMI. Obesity is one component contributing to OSA hence with increasing prevalence of obesity the prevalence of OSA is also increasing.
Sleep latency (ability to stay awake)	Mean sleep latency was 12-13 minutes as measured using the MWT. Sleep latency is not usually assessed in routine clinical practice.
ESS Score	Mean baseline ESS scores were approximately 15 (range of mean ESS scores across arms were 14.8 to 15.6). This is slightly higher than that of the population that would be treated for residual EDS in England and Wales. The ERG's clinical experts indicated that patients would probably be reviewed regarding residual EDS at a lower ESS threshold, but for treatment to be initiated, an ESS in the moderate to severe range (ESS>14) or a severe complaint of sleepiness would be preferred. One expert did not think the difference from UK experience was clinically significant.
Severity of EDS	Most patients (91% in TONES 3 and 85% in TONES 4) were at least moderately ill (according to their baseline CGI-s score).
Primary OSA therapy compliance	Approximately 70% of participants (range 68.4- 72.6% among placebo and licenced solriamfetol doses) were compliant with their primary OSA therapy. This is higher than the clinical experts consulted by the ERG would expect in routine practice, where compliance with primary therapy may only be about 50%.
EQ-5D-5L index score	In TONES 3, mean (SD) baseline EQ-5D-5L index scores were high (placebo [redacted] and solriamfetol [redacted]) with a proportion of participants having a utility score of 1 at baseline (placebo [redacted], solriamfetol arms [redacted]) suggesting no or little disutility. EQ-5D-5L index scores were not an outcome in TONES 4.

Source: Compiled by ERG using information presented in CS Tables 7, 9 and CS section.2.6.1.10.
CGI-s, Clinician global impression of severity for which investigators rated their impression of the patient's symptom severity.

In both TONES 3 and TONES 4 the reported baseline characteristics were broadly similar across trial arms. For TONES 5 the baseline characteristics of the participants with OSA are reported as a single combined solriamfetol group (i.e. regardless of the solriamfetol dose they were receiving). For the TONES 5 participants who were enrolled in the randomised withdrawal phase CS section B.2.3.2.2.2 states that the baseline disease characteristics were generally similar to the population of the open-label period. However, baseline characteristics are not tabulated in the CS for the two arms of the TONES 5 randomised withdrawal phase.

ERG conclusion on included studies

The TONES 3 trial is an appropriate main source of clinical effectiveness evidence for this appraisal. A higher proportion of the TONES 3 trial population was compliant with primary OSA therapy and baseline ESS may have been slightly higher than would be expected in typical practice, but this is probably not clinically significant. In all other respects the TONES 3 trial population is broadly similar to the patient population seen in the NHS. The TONES 4 and TONES 5 trials both report the effects of a randomised withdrawal from solriamfetol treatment, with TONES 5 also providing open-label longer-term data on efficacy and safety of solriamfetol.

3.2.3 Risk of bias assessment

3.2.3.1 TONES 3 and TONES 4 trials

The company assessed the risk of bias in the TONES 3 and TONES 4 trials using NICE recommended criteria (CS section B.2.5 and Appendix D.2). The ERG independently assessed risk of bias using these criteria and agreed that the trials are of good methodological quality and low risk of bias (Table 6).

Table 6 Risk of bias assessment in TONES 3 and TONES 4 trials

Trial ID	TONES 3		TONES 4	
	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
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[a]	Yes	Yes[a]
Does treatment administration reflect recommended clinical practice (i.e., initial dose and titration)?	No	No	No	No

Source: Adapted from CS Table 12
[a] Sleep aids and stimulants that could affect the evaluation of excessive sleepiness were not permitted but patients could take their other usual medications.

The following minor issues were identified:

- The modified intention-to-treat (mITT) analysis used in TONES 3 and TONES 4 comprised all patients who received ≥1 dose of study drug, had a baseline (or pre-withdrawal phase) measurement of ESS or MWT and at least one post-baseline evaluation of ESS or MWT. As 5% or less of randomised patients were excluded from the mITT in these trials, any bias arising from their exclusion is likely to be low.
- In TONES 3, overall, 12% of the mITT population did not complete the study. The percentage of patient withdrawals in the mITT population varied between the placebo, 37.5 mg, 75 mg, 150 mg and 300 mg dose arms ([redacted] and [redacted] respectively). A higher proportion of withdrawals was observed in the unlicensed 300 mg dose arm chiefly because of a higher incidence of withdrawals due to adverse events (AEs) in this arm (n=[redacted] vs n=[redacted] across the other arms). Within the licensed dose arms, there was no evidence of any systematic reason for imbalances in drop-out rates between trial arms. Lack of efficacy was not reported as a reason for withdrawal in any solriamfetol arm. The ERG conclude that it is unlikely that the slight imbalance in withdrawals between groups would cause a significant risk of bias.
- [redacted]

  [redacted] The ERG concludes that missing data for the primary efficacy outcomes were handled appropriately and were unlikely to have introduced significant bias. For the secondary outcomes of the Patient and Clinician Global Impression of Change scores (PGI-c and CGI-c, see section 3.2.4.1, only single rather than multiple

imputation methods were used, however the most conservative of these methods [redacted] (which used the [redacted] method). For these outcomes there remains some uncertainty as to the likely impact of missing data on results since the amount of missing data is not fully reported and furthermore the definition of 'worst-case scenario' is not full elaborated in the CSR.

The company included two additional items in their risk of bias assessment concerning 1) whether use of concomitant therapies was permitted during the study and 2) the extent to which the study dosing regimen reflected clinical practice. The ERG notes that these two items do not assess the risk of bias in terms of the internal validity of the study, rather they assess its external validity (generalisabilty).

1. The ERG note that patients were permitted to use concomitant medications with the exception of medicines that may aid sleep or the ability to influence assessment of sleepiness. In practice, patients may have other comorbidities such as pain, depression, anxiety and may use medicines for such conditions that can cause drowsiness. The ERG therefore notes that the trial may not be fully representative of clinical practice in this respect.
2. We also note that the dosing regimen used in the TONES trials were driven by the respective trial protocols. Solriamfetol doses were titrated from a higher starting dose (75 mg) than the starting dose that is currently recommended in the product's licence (37.5 mg). It is unclear how the dose will be titrated in practice and there could be a trade-off between the dosing schedule and clinic frequency. Clinical expert advice to the ERG noted that the 37.5 mg dose appears to be less effective. Two possible approaches to dose titration were suggested:
    - One expert thought clinicians might issue an initial prescription for 75 mg daily for 4-6 weeks but would advise the patient to begin treatment at 37.5 mg daily for one week, then if EDS persisted and providing there were no side-effects from treatment, the patient would self-titrate to 75 mg daily before returning to the clinic for review at 4-6 weeks. At this point there could be further titration to the 150 mg dose.
    - A second expert thought it possible that the 75 mg dose may be used as a starting dose particularly once clinical experience is gained prescribing solriamfetol in practice. (Note that this is not a recommended starting dose for solriamfetol in the OSA SmPC).

3.2.3.2 TONES 5 study

As described earlier, TONES 5 was a long-term, open-label extension safety and maintenance of efficacy study with no comparator to solriamfetol, 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 Appendix D.2). The checklist includes criteria that primarily cover the quality of the conduct and reporting of the study, with some criteria covering risk of bias (e.g. blinding of study personnel during the randomised withdrawal phase).

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).

ERG conclusion on risk of bias

The ERG agrees with the company's view that that the TONES 3 and TONES 4 trials are of good methodological quality and at low risk of bias in terms of internal validity. We also agree that TONES 5 was well conducted but note the potential for bias due to the lack of comparator arm in the longer term open-label phase of this study.

3.2.4 Outcomes assessment

3.2.4.1 Efficacy outcome(s)

The main efficacy outcome of interest included in the NICE scope is EDS. Two different efficacy measures were used in the TONES trials:

- The Epworth Sleepiness Scale (ESS) which measures **excessive daytime sleepiness (EDS)**
- The Maintenance of Wakefulness Test (MWT) which measures **wakefulness** (the patients' ability to remain awake).

TONES 3 RCT

Table 7 summarises the primary and secondary efficacy outcomes measured in the TONES 3 trial while Table 8 provides the ERG critique of these outcome measures

Table 7 Primary and secondary outcomes in TONES 3

Outcome type	Outcome definition
Epworth sleepiness scale (ESS) score:	
Co-primary efficacy	Change from baseline to week 12
Secondary efficacy	Change from baseline to weeks 1, 4 and 8
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)
Secondary efficacy	MWT40 change from baseline to week 1 and 4
	Time course of efficacy on MWT: Change in sleep latency time[a] (minutes), at week 12, on each of a series of five 40-minute MWT trials.
Patient Global Impression of change (PGI-c) score:	
Key secondary efficacy	Percentage of patients who reported improvement at week 12
Secondary efficacy	Percentage of patients who reported improvement at weeks 1, 4 and 8
Clinician Global Impression of change (CGI-c) score:	
Secondary efficacy	Percentage of clinicians reported as improved at weeks 1, 4, 8 and 12.

Source: CS Table 5

[a] sleep latency is a measure of the time taken to fall asleep (see Table 8 of this ERG report)

Table 8 ERG critique of outcome measures: TONES 3

Outcome measure description	ERG comments
Epworth sleepiness scale (ESS) score:	
• Patients rate the level of sleepiness they experienced over the [redacted], using the questionnaire validated for this duration. • Patients asked how likely they would be to doze off or fall asleep in eight different situations. • Total scores range from 0–24; higher scores represent more severe sleepiness. • Scores ≤10 considered within normal range. • A minimal clinically important difference (MCID) in ESS score of 2 to 3 points has been defined in OSA patients [8] • ≥3-point reduction used to define response for the company's base case economic model (CS Section B.3.3.3)	• Subjective, validated patient self-assessment tool[9 10] • Clinical experts reported that, whilst the ESS is used in practice, this is not relied upon as the sole measure of monitoring patients. Clinical judgement and broader assessment of symptomatic improvement of EDS, activities of daily living, quality of life and social impact would also be considered in practice. • Clinical experts generally agreed with assumption that a 3-point reduction is clinically relevant for patients It is unclear from the CS what between-group difference (i.e. between solriamfetol and placebo) would be considered clinically important. Clinical expert advice to the ERG suggests that a 2- to 3-point difference in mean ESS score between groups would be considered clinically relevant.
Maintenance of wakefulness test (MWT), change in mean sleep latency time (minutes), from baseline to endpoint:	
• Validated objective assessment of the ability of a participant to remain awake.	• Clinical experts report this is not used extensively to monitor treatment response in practice.

Outcome measure description	ERG comments
• Measurement subsequent to an overnight stay at the study site for nocturnal polysomnography (PSG) according to a standard protocol. • Measurements of sleep latency using the MWT40 range from 0 to 40 minutes. • Scores >19.4 minutes are above the lower limit of normal • A positive change from baseline represents an improvement.	• References to validation studies have been provided.[11-13] • The ERG notes that a minimally detectable change relative to placebo of 5 minutes was considered as per the sample size calculation provided in CS Table 11. It is unclear whether 5 minutes is likely to be clinically important. In response to clarification question A2, the company report that a clinically relevant change in MWT has not been established but consider 5 minutes to be greater than what has been observed with other drugs to treat excessive daytime sleepiness associated with OSA. (e.g. modafinil).
Patient and Clinician Global Impression of change (PGI-c & CGI-c) scores:	
• Patients or clinicians respectively rate the change in patient's 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.	• This outcome has been dichotomised to 'improved' (score of 3 or less) or 'worsened' (score of 5 or more). • Degree of improvement or worsening not fully captured by dichotomised score (i.e. all changes could be minimal).

Source: CS Table 5 and Table 6

Additional post-hoc and exploratory outcomes are described in CS Table 5. Of note, these exploratory outcomes include two endpoints measuring changes in primary OSA therapy from baseline to weeks 9-12. These are defined as the mean change in the percentage of nights patients used a primary OSA therapy and, for patients with electronically retrievable data, the mean change in average number of hours per night patients used their OSA device.

Post-hoc analyses also include the percentage of patients achieving normalisation of ESS score (ESS≤10) as an alternative measure of treatment response. In addition, the ERG requested that the company provide the proportion of patients in each TONES 3 trial arm who achieved a reduction from baseline in ESS score of ≥ 3-points at week 12, with corresponding p-values for each pairwise comparison between groups (see clarification question A8).

TONES 4 RCT

In TONES 4 the primary co-efficacy outcomes were mean change in ESS and MWT40 from the end of the stable dose phase (week 4) to the end of the withdrawal phase (week 6). Secondary efficacy outcomes included the percentage of patients reported as worse (assessed by PGI-c and CGI-c scores of minimally worse, much worse or very much worse)

at the end of the withdrawal phase (week 6) (CS Table 5). The ERG considers these outcome measures to be appropriate.

TONES 5 study

In the open label phase of TONES 5, ESS, PGI-c and CGI-c were measured at various time points (Table 9). 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 2-week randomised-withdrawal period. The ERG considers these outcome measures to be appropriate.

Table 9 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 8 and Figure 9

[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; [c] minimally, much or very much worse

3.2.4.2 HRQoL outcomes

Change from baseline in a range of different HRQoL measures were used in TONES 3 (at week 12) and TONES 5 (at the same time points 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), visual analogues scales (VAS) AS and index values. Definitions for the HRQoL outcomes are provided in CS Table 6. However, none of the trial based HRQoL outcomes inform the base case economic model for reasons we discuss later in this report (Section 4.2.7.1).

3.2.4.3 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 (heart rate and blood pressure); and potential for abuse or withdrawal effects. Discontinuation rates due to TEAEs and discontinuation due to loss/lack of efficacy reported in TONES 3 and TONES 5 are used the company's economic model (CS Section B.3.3.8 and B.3.3.9). The ERG considers the choice of safety outcomes to be appropriate and relevant to the OSA population.

3.2.4.4 Contribution of data from clinical effectiveness studies to economic model

TONES 3 was the key contributor of clinical evidence for the economic model (Table 10). Data from TONES 5 were primarily used to estimate discontinuation rates due to adverse events or loss of efficacy over an extended time period (CS sections B.3.3.8 and B.3.3.9).

Table 10 Contribution of outcome data to company's economic model

STUDY	OUTCOME	USE IN ECONOMIC MODEL
TONES 3 RCT	ESS (co-primary efficacy) – change from baseline to week 12	Week 12 IPD used for response estimate for solriamfetol to estimate the proportion of responders and the average change in ESS from baseline in each treatment arm (CS section B.3.3.3 and B.3.3.4)
	Discontinuations due to loss of response	Used in the calculation of discontinuation due to loss of response within the initiation phase of treatment (first 12 weeks). (CS section B.3.3.8)
	Discontinuation due to TEAEs	Used in the calculation of discontinuation due to TEAEs within the initiation phase of treatment (first 12 weeks). (CS section B.3.3.9)
TONES 5 open label	Discontinuation due to loss of response	Used to estimate discontinuation rates due to loss of response in the maintenance treatment phase (CS section B.3.3.8)
	Discontinuation due to TEAEs	Used to estimate discontinuation rates due to TEAEs in the maintenance treatment phase (CS section B.3.3.9)

IPD: individual patient data; TEAEs; treatment emergent adverse events

The withdrawal phase of TONES 4 and 5 indicated that ESS scores would increase after solriamfetol discontinuation but not to baseline levels (CS Figures 12 and 13). The company conservatively assumed however an immediate return to baseline after discontinuation.

ERG conclusion on outcomes assessment

The CS includes a mixture of (subjective) patient- and investigator-reported outcomes used to assess sleepiness symptoms; disease-specific and generic instruments to measure HRQoL; and (objective) standard polysomnographic

monitoring of patients' ability to remain awake (sleep latency). The measures used have been validated in the published literature, and some (such as the ESS) are used in clinical practice but would be used in combination with broader clinical assessment. Dichotomising the PGI-c and CGI-c scores could mean the degree of improvement or worsening has not been fully captured and there is a lack of evidence to support the company's assumptions about the minimal important clinical differences between treatment and placebo.

3.2.5 Approach to study statistics

In Table 11 below we summarise and critique the statistical methods used in the TONES OSA studies. Further detail on these methods can be found in the CS (Section B.2.4).

Table 11 ERG critique of statistical methods used in the TONES studies

TONES-3	TONES-4	TONES-5 (withdrawal phase)[a]
ANALYSIS POPULATIONS		
Three analysis sets are defined for each of the three TONES OSA studies (CS Table 10): 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 3 and TONES 4) and for the analyses of the randomised-withdrawal phase (TONES-5). In general terms, the mITT populations comprised patients who received ≥1 dose of study drug and had a baseline and ≥1 post-baseline evaluation of a primary outcome (TONES 3 and TONES 4) or other efficacy data (TONES 5) after randomisation.		
ERG comment: The proportions of randomised patients excluded from the mITT population in each trial were small ≤5%; and unlikely to introduce significant bias to results. The mITT is an appropriate analysis population for the primary outcomes in the TONES trials.		
SAMPLE SIZE CALCULATIONS		
The planned sample size (55 patients in the solriamfetol 37.5 mg and 75 mg groups and 110 patients in the placebo and solriamfetol 150 mg and 300 mg groups) was reached in the mITT population (Appendix D.1.1 Figure 1).	The planned sample size for the randomised withdrawal phase (61 patients randomised to placebo, 61 to remain on maximum tolerated solriamfetol dose) was reached in the mITT population (Appendix D.1.2 Figure 2).	The sample size appears to be based on the combined OSA and narcolepsy populations included in this study. Approximately 300 patients (divided 1:1 placebo or maximum tolerated solriamfetol dose) was estimated to be sufficient.
ERG comment: The sample size calculations for the TONES trials to be appropriate. Adequately powered sample sizes were achieved in the mITT populations.		

TONES-3	TONES-4	TONES-5 (withdrawal phase)[a]
METHODS TO ACCOUNT FOR MULTIPLICTY[a]		
Fixed hierarchical testing was used for the co-primary outcomes and the key secondary outcome [redacted] For analyses that were not part of the prespecified hierarchical analysis there were no multiplicity adjustments. The CS and the response to clarification question A3 state p-values presented for these analyses are considered nominal.	Fixed hierarchical testing was used starting with a comparison of combined solriamfetol vs placebo for the co-primary efficacy endpoints, followed by PGI-c if both co-primary endpoints were significant. [redacted]	A fixed hierarchical testing sequence started with ESS and proceeded to PGI-c and CGIc if the primary endpoint was significant. 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).
ERG comment: The methods used to account for multiplicity are sufficient and appropriate.		
ANALYSIS OF OUTCOMES		
MMRM model used to analyse: Co-primary outcomes other ESS and MWT endpoints, FOSQ-10, SF36v2, EQ VAS, EQ-5D-5L Index, WPAI:SHP.	[redacted]: Co-primary endpoints [redacted]	[redacted]: Primary outcome of randomised withdrawal phase [redacted].
Chi-squared tests used to analyse PGI-c, CGI-c and EQ-5D-5L Dimensions	Withdrawal phase: Chi-squared tests used to analyse PGI-c and CGI-c	Withdrawal phase: Chi-squared tests used to analyse PGI-c and CGI-c
ERG comment: The analysis methods were considered appropriate to the types of outcomes measures.		
[redacted]		
Primary endpoints – MMRM model [redacted]. [redacted] Other endpoints – MMRM model.	Primary endpoints – missing data imputed using LOCF. [redacted]	[redacted]
ERG comment: The use of the MMRM is appropriate to account for missing data when measuring treatment effects over multiple time points. [redacted]		

TONES-3	TONES-4	TONES-5 (withdrawal phase)[a]
SENSITIVITY & POST-HOC ANALYSES		
- [redacted]	[redacted]	[redacted]
Post-hoc analysis of patients achieving normal ESS and MWT values (mITT population using LOCF approach)	No post-hoc analyses listed in CS Table 11	Post-hoc analysis of patients achieving normal ESS values (LOCF approach)
ERG comment: We note that for some outcomes only a single imputation method such as LOCF was used to account for missing data which may be prone to bias (see section 3.2.3). Post-hoc analyses were appropriate and in line with clinical advice to the ERG that normalisation of ESS may be an appropriate alternative measure of treatment response.		

Source: CS Table 11
ANCOVA = Analysis of covariance; LOCF = Last observation carried forward; MMRM = Mixed-effect model with repeated measures
[a] The withdrawal phase was the randomised phase of TONES 5
[b] Multiplicity may arise due to multiple doses and endpoints studied and has potential to find significant results by chance when no underlying effect exists

ERG conclusion on approach to study statistics

The statistical methods used in the TONES OSA studies are clearly summarised 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 and sensitivity analyses tested alternative approaches. Appropriate methods were used 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

3.2.6 Results from clinical effectiveness studies

3.2.6.1 Key efficacy results from TONES 3, TONES 4 and TONES 5 trials

In this section we report on the primary outcomes and selected secondary outcomes from the TONES 3, TONES 4 and TONES 5 trials. Note that data presented for TONES 5 results are for the subgroup of patients with OSA only. This includes change from baseline in the

following outcome measures: ESS score, mean sleep latency (MWT) and PGI-c score. We also report on change in use of primary OSA therapy (an exploratory outcome) which has been identified as a potential concern by the clinical experts we consulted. We do not report on all PGI-c and CGI-c secondary outcomes, post-hoc analyses or exploratory polysomnography outcomes which are summarised narratively by the company in the CS.

3.2.6.1.1 ESS

TONES 3 Co-primary efficacy endpoint

In TONES 3, the primary analysis was conducted for the mITT population: licensed doses of solriamfetol 37.5 mg (N=56), 75 mg (N=58), solriamfetol 150 mg (N=116) and placebo (N=114). Statistically significant improvements were reported for change in ESS (one of the co-primary efficacy outcomes) for all solriamfetol doses at week 12 (Table 12).

The mean improvement in ESS score from baseline to week 12 in all trial arms (including placebo) exceeded -3 and would therefore be considered clinically significant. In response to clarification question A8 the company reported the proportion of patients who achieved a reduction from baseline in ESS score of ≥3-points at week 12 (Table 12). The greatest proportion of patients with a change from baseline ESS of ≥3 occurred in the solriamfetol [redacted] group ([redacted]) whereas in the other two solriamfetol groups the proportion was just over [redacted]. In the placebo group [redacted] of patients had a change from baseline ESS of ≥3. We discuss the interpretation of a possible placebo effect in section 4.2.3 and section 4.2.6 of this report, in relation to assumptions informing the economic model.

Table 12 Effects of solriamfetol on change in ESS compared to placebo at week 12 (TONES 3)

Co-primary outcome: Change in ESS from baseline	Placebo (N=114)	Solriamfetol 37.5 mg (N=56)	Solriamfetol 75 mg (N=58)	Solriamfetol 150 mg (N=116)
LS mean (SE)	-3.3 [redacted]	-5.1 [redacted])	-5.0 [redacted]	-7.7 [redacted]
LS mean difference (95% CI, p-value) relative to placebo	-	-1.9 (-3.4 to -0.3), p=0.0161	-1.7 (-3.2 to -0.2, p=0.0233)	-4.5 (-5.7 to -3.2, p<0.0001)
Proportion of patients with a change from	[redacted]	[redacted]	[redacted]	[redacted]

baseline ESS of ≥3 at week 12				
p- value for placebo vs treatment[a]	Not applicable	[redacted]	[redacted]	[redacted]

Source: CS Table 13 and company response to clarification question A8
[a] nominal p-values only for each pairwise comparison as these tests were not specified a-priori

In CS Section B.2.6.1.5.1 the company specified that a 2- to 3-point difference in change from baseline ESS score between solriamfetol and placebo would be considered a minimal clinically important difference (MCID). However, in response to clarification question A8, the company state that the correct interpretation is that the observed changes from baseline ESS score exceed this minimally important difference of 2-3 points and thus no longer refer to this MCID as being applicable to the differences between the solriamfetol groups and placebo. Subsequent clinical expert advice to the ERG, however, suggests that the same 2- to 3-point difference may also be considered as clinically meaningful in terms of the between group difference. The ERG notes that such a difference was not achieved for the comparisons between the 37.5 mg and 75 mg doses respectively and placebo.

TONES 3 secondary ESS endpoints:

In TONES 3, ESS also improved at weeks 1, 4 and 8 relative to baseline in all four trial arms (CS Figure 5) with greatest improvement seen for the 150 mg solriamfetol dose. Compared to placebo, statistically significant differences in the change in ESS from baseline were consistently observed at all time points for the 75 mg and 150 mg doses only (CS Figure 5). For the 150 mg dose, the improvements in ESS compared to placebo exceeded -3 at all time points which would also be considered clinically significant.

TONES 3 post-hoc ESS outcome: normalisation of ESS score

A possible source of uncertainty is the choice of measure of treatment response. Some clinical experts (to both the ERG and KOL consulted by the company) commented that normalisation of the ESS score (≤10) may be considered as the ideal treatment outcome. The CS describes normalisation of ESS score in a post-hoc analysis (CS B.2.6.1.5.3) in TONES 3. At week 12, a higher proportion of patients achieved normalisation of ESS score in the solriamfetol groups (51.8%, 55.2% and 70.7% for the 37.5 mg, 75 mg and 150 mg doses respectively) compared to placebo (37.7%).

TONES 4 and TONES 5: ESS results from randomised withdrawal phase:

TONES 4 and TONES 5 were different in design to TONES 3 but both contained a randomised withdrawal phase. TONES 4 comprised a 2-week open label dose titration

phase (from 75 mg daily up to maximum of 300 mg daily), a 2-week stable dose phase and a 2-week placebo-controlled randomised withdrawal phase in which patients were randomised to either remain on their stable dose of solriamfetol or switch to placebo. The primary analysis was conducted for the mITT population: solriamfetol all doses combined (N=60) and placebo (N=62). TONES 5 also included a 2-week placebo-controlled randomised withdrawal phase following at least 26 weeks of open-label solriamfetol treatment. Patients were randomised to either continue solriamfetol treatment (75 mg, 150 mg and 300 mg dose groups combined, N=101) or placebo (N=101). Key ESS results are summarised in Table 13. Full results for TONES 4 are presented in CS Section B.2.6.3 and for TONES 5 in CS Section B.2.6.2.3.

In both studies, patients randomised to remain on solriamfetol treatment (all doses combined) did not experience a large change in ESS indicating treatment benefit was maintained. In contrast, patients randomised to switch to placebo experienced a deterioration (increase of >4 points) in ESS score (Table 13).

Table 13 Key efficacy results for ESS from randomised withdrawal phase of TONES 4 and TONES 5

Outcome	TONES 4		TONES 5	
	Placebo (n=62)	**Solriamfetol, all doses (n=60)**	**Placebo (n=101)**	**Solriamfetol, all doses (n=101)**
Mean change (SE) in ESS score from the end of the stable dose phase to the end of the withdrawal phase	+4.5 (0.7)	-0.1 (0.67)	[redacted]	[redacted]
LS mean difference for solriamfetol vs placebo (95% CI), p value	-	-4.6 (-6.4 to -2.8), p<0.0001		[redacted]

Source: Text in CS B.2.6.2.3.1 and CS B.2.6.3.1

TONES 5: ESS Results from open-label phase

TONES 5 (CS Section B.2.6.2.2) was predominantly a longer-term (up to 1 year) open-label study enrolling patients with OSA (N=417) who had participated in previous solriamfetol trials (including TONES 3 and TONES 4) (the randomised withdrawal component results described above were just a part of the wider TONES 5 study). TONES 5 also enrolled patients with narcolepsy who are not reported on in the current CS.

Participants with OSA in TONES 5 enrolled from TONES 3 with no break in treatment. Changes in ESS for these participants are reported with respect to the baseline in TONES 3. Participants from TONES 4 may have had a break in solriamfetol treatment before enrolling in TONES 5, so for these participants changes in ESS are reported with respect to the TONES 5 baseline:

- In both group A and group B, improvements in ESS were observed from week 2 of treatment for both solriamfetol doses and were maintained over time (Table 14).
- Mean change from baseline ESS at final assessment: ranged from [redacted] (Group A at week 40) to [redacted] (Group B at week 52) for the 75 mg modal dose and [redacted] to [redacted] for the 150 mg modal dose relative to baseline. The ERG notes that only [redacted] of enrolled OSA patients (N=417) contributed to these analyses. Although not explicitly stated it is likely the remaining participants of TONES 5 received the 300 mg solriamfetol dose.

The CS reports ESS data over time for the combined solriamfetol doses (including 300 mg) in CS Figures 8 and 9 and text in CS Section B.2.6.2.2.1. It should be noted that for the open label phase of TONES 5 the changes in ESS are not controlled by a placebo group.

Table 14 TONES 5 change in mean ESS scores from baseline for patients with OSA for the solriamfetol 75 mg and 150 mg dose (Safety population)

Change from baseline (SD)[a]	Group A (from TONES 3)		Group B (from TONES 4)	
	75 mg [redacted]	150 mg [redacted]	75 mg [redacted]	150 mg [redacted]
At week 2	[redacted]	[redacted]	[redacted]	[redacted]
At week 40	[redacted]	[redacted]	NA	NA
At week 52	NA	NA	[redacted]	[redacted]

Source: CS Table 15
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.

3.2.6.1.2 MWT

TONES 3 Co-primary efficacy endpoint

In TONES 3, statistically significant improvements were reported for the change in MWT (co-primary efficacy outcome) for all solriamfetol doses at week 12 (Table 15). There was little change in MWT time at 12 weeks among placebo group participants. The effects of solriamfetol were dose-dependent with more modest effects observed on MWT for the

37.5 mg and 75 mg doses. In response to clarification question A2 the company states that clinically meaning differences for the MWT have not been well established, but they state that a 5-minute difference is greater than what has been observed with other drugs for this indication.

Table 15 Effects of solriamfetol on change in MWT compared to placebo at week 12 (TONES 3)

Co-primary outcome: Change in MWT from baseline	**Placebo (N=114)**	**Solriamfetol 37.5 mg (N=56)**	**Solriamfetol 75 mg (N=58)**	**Solriamfetol 150 mg (N=116)**
LS mean (SE)	0.2 ([redacted])	4.7 ([redacted])	9.1 ([redacted])	11.0 ([redacted])
LS mean difference (95% CI, p-value) relative to placebo (minutes)	-	4.5 (1.2 to 7.9), p=0.0086	8.9 (5.6 to 12.1), p<0.0001)	10.7 (8.1 to 13.4 p<0.0001)

Source: CS Table 13

TONES 3 secondary MWT endpoints:

- MWT also improved at weeks 1, 4 and 8 relative to baseline in all four trial arms (CS Figure 6) with greatest improvements seen for the 150 mg solriamfetol dose. Compared to placebo, statistically significant differences in the change in MWT from baseline were consistently observed at all time points for the 75 mg and 150 mg doses only (CS Figure 6).
- Changes from baseline in sleep latency as measured by the MWT were consistently greater and statistically significant for solriamfetol 75 mg and 150 mg compared to placebo in each of the five individual tests taken at 2 hour intervals throughout the day at week 12 (CS Figure 7) starting from within one hour of dosing. These effects were not sustained throughout the day for the 37.5 mg solriamfetol dose.

TONES 4 and TONES 5: MWT results from randomised withdrawal phase

In keeping with the analysis of ESS scores, patients switching to placebo had a greater deterioration in MWT (-12.1 minutes) compared to those remaining on solriamfetol (-1.0 minutes) in TONES 4 during the randomised withdrawal phase (Table 16). MWT was not measured in TONES 5.

Table 16 MWT results from the randomised withdrawal phase of TONES 4

Outcome: MWT (minutes)	TONES 4	
	Placebo (n=62)	Solriamfetol, all doses (n=60)
Mean change (SE) from the end of the stable dose phase to the end of the withdrawal phase	-12.1(1.3)	-1.0 (1.4)
LS mean difference for solriamfetol vs placebo (95% CI), p value	-	11.2 (7.8 to 14.6), p<0.0001

Source: Text in CS B.2.6.3.1

3.2.6.1.3 PGI-c score

- In TONES 3, 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 (55.4% for 37.5 mg, 72.4% for 75 mg and 89.7% for 150 mg) compared to placebo (49.1%). Statistical significance was declared for the 75 mg and 150 mg doses vs placebo.
- In the randomised withdrawal phases of TONES 4 and TONES 5, a higher proportion of patients reported worsening of their PGI-c score after switching to placebo than in those who remained on solriamfetol treatment in both studies (Table 17).
- In the open label phase of TONES 5 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 >90% of patients at the final assessment.

Table 17 PGI-c score from randomised withdrawal phase of TONES 4 and TONES 5

Outcome: PGI-c score	TONES 4		TONES 5	
	Placebo (n=62)	Solriamfetol, all doses (n=60)	Placebo (n=101)	Solriamfetol, all doses (n=101)
% reporting worse (minimally, much or very much worse) PGI-c score at the end of the withdrawal phase	50.0	20.0	[redacted]	[redacted]
p value versus placebo	-	p<0.005	-	[redacted]

Source: CS Table 17 and text in CS B.2.6.2.3.2

3.2.6.1.4 Exploratory outcome: Change in use of primary OSA therapy

Clinical experts consulted by the ERG expressed concern that some patients with OSA and EDS may favour the relative simplicity of taking a drug treatment for their symptoms over using primary OSA therapy such as CPAP devices. This could lead to a reduction in

compliance with such devices and negate the benefits associated with their use. Patients' use of primary OSA therapy was monitored as an exploratory endpoint during the three TONES trials.

TONES 3

In TONES 3, for participants for whom data were available, no meaningful changes from baseline to weeks 9-12 were found in the percentage of nights that patients used primary OSA therapy or the average number of hours per night that patients used their OSA device (Table 18). The CS and CSR do not clearly state which patients were included in this analysis. The ERG assumes that this analysis included a sub-group of TONES 3 patients for whom a baseline and week 9-12 measurement for device use were available. The analysis does not appear to be restricted to patients who were compliant at baseline. The ERG notes that similar proportions of patients in placebo and solriamfetol groups did not have electronically retrievable data however this amounted to over a third of patients. It is possible therefore that those patients excluded from the analysis may have a different pattern of OSA device use. Furthermore, patterns of primary OSA device usage in the controlled clinical trial setting may differ from that in real-world setting and it is not known whether the continued use of OSA devices could vary according to level of compliance with OSA device therapy at baseline.

Table 18 Change in use of primary OSA therapy during TONES 3

Study (endpoint)	**Change from baseline in:**			
	Percentage of nights of primary OSA therapy usage		**Average no. of hours per night of primary OSA therapy usage**	
	Placebo (n=69)	**Solriamfetol all doses (n=218)[a]**	**Placebo (n=43)[b]**	**Solriamfetol all doses (n=133)[a,b]**
TONES 3 (change from baseline to weeks 9-12)	0.8%	1.1%	A mean reduction of 0.3 hours per night was observed in both groups	

Source: Table prepared by ERG with information from CS Section B.2.6.1.8
[a] This includes participants randomised to the unlicensed 300 mg solriamfetol dose.
[b] For patients with electronically retrievable data

TONES 4

With respect to use of primary OSA therapy devices, minimal changes were also observed in TONES 4 from the start to the end of randomised withdrawal period (Table 19).

Table 19 Change in use of primary OSA therapy during the randomised withdrawal phase of TONES 4

Study (endpoint)	Change from baseline in:			
	Percentage of nights of primary OSA therapy usage		Average no. of hours per night of primary OSA therapy usage	
	[redacted]	[redacted]	[redacted]	[redacted]
TONES 4 (mean change from start to end of randomised withdrawal phase)	[redacted]	[redacted]	[redacted]	[redacted]

Source: Table prepared by ERG with information from CS Section B.2.6.3.7 and TONES 4 CSR Section 11.4.4.2

TONES 5

Full details for TONES 5 of the changes in primary OSA therapy use over the course of the randomised withdrawal period and the change in use during the longer term open label period (up to 40/52 weeks) are reported in the CSR sections 11.4.1.1.3.2 and 11.4.1.2.5 and are not elaborated here. [redacted]

3.2.6.2 HRQoL outcomes

In TONES 3, 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 37.5 mg, 75 mg and 150 mg versus placebo at week 12 are reported in CS Table 14 and in the company's response to clarification question A9. In addition, change in the total score using the disease-specific FOSQ-10 from baseline to week 12 and mean difference for the three solriamfetol doses versus placebo were also reported (CS Table 14). Among the generic HRQoL measures Among the generic HRQoL measures only scores on the SF-36v2 and EQ-5D VAS improved numerically for all solriamfetol doses but the only statistically significant improvements in comparison to placebo were obtained using the SF-36v2 in the 150 mg solriamfetol group (Table 20). Numerical improvements using the disease-specific FOSQ-10 were obtained but again the change from baseline at week 12 in comparison to placebo was only statistically significant for the 150 mg solriamfetol dose.

The company notes the lack of significant change in EQ-5D-5L scores and provide justification of their use of an alternative HRQoL tool to calculate utilities in the economic model in CS Section B.3.4.

Table 20 TONES 3: HRQoL endpoints (mITT Population)

	Placebo N=114	Solriamfetol 37.5 mg N=56	Solriamfetol 75 mg N=58	Solriamfetol 150 mg N=116
Change in FOSQ-10 total score from baseline to week 12				
LS mean (SE)	1.72 (0.241)	1.99 (0.345)	2.47 (0.331)	2.95 (0.236)
LS mean difference vs. placebo		[redacted]	[redacted]	[redacted]
95% CI		[redacted]	[redacted]	0.57, 1.88
p value		[redacted]	[redacted]	[redacted]
Change in SF-36v2 physical component summary score from baseline to week 12				
LS mean (SE)	1.43 (0.608)	1.64 (0.876)	1.99 (0.838)	3.50 (0.598)
LS mean difference vs. placebo		[redacted]	[redacted]	2.07
95% CI		[redacted]	[redacted]	0.42 to 3.72
p value (nominal)		[redacted]	[redacted]	[redacted]
Change in SF-36v2 mental component summary score from baseline to week 12				
LS mean (SE)	1.05 (0.703)	2.65 (1.012)	2.94 (0.965)	3.10 (0.691)
LS mean difference vs. placebo		[redacted]	[redacted]	2.05
95% CI		[redacted]	[redacted]	0.14 to 3.96
p value (nominal)		[redacted]	[redacted]	[redacted]
Change in EQ-5D-5L Index from baseline to week 12 [a]				
LS mean (SE)	0.02 (0.009)	0.01 (0.012)	0.02 (0.012)	0.03 (0.008)
LS mean difference vs. placebo		-0.01	0.00	0.01
95% CI		-0.04 to 0.02	-0.03 to 0.03	-0.02 to 0.03
p value		[redacted]	[redacted]	[redacted]

	Placebo N=114	Solriamfetol 37.5 mg N=56	Solriamfetol 75 mg N=58	Solriamfetol 150 mg N=116
Change in EQ-VAS from baseline to week 12				
LS mean (SE)	2.4 [redacted]	3.4 [redacted]	4.0 [redacted]	4.9 [redacted]
LS mean difference vs. placebo		[redacted]	[redacted]	[redacted]
95% CI		[redacted]	[redacted]	[redacted]
p value		[redacted]	[redacted]	[redacted]

Source: Reproduced from CS Table 14 (footnotes edited) & response to clarification question A9
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.

In the randomised withdrawal phase of TONES 4, mean FOSQ-10 scores were reported to be significantly worse in the placebo group after withdrawal from treatment compared to those who continued on solriamfetol [16.4 (SD 2.9) vs 17.4 (SD 3.0), least squares mean difference: 1.2, p<0.05, CS Section B.2.6.3.5). Similarly In the randomised withdrawal phase of TONES 5, mean FOSQ-10 scores were also reported to be [redacted] in the placebo group after withdrawal from treatment compared to those who continued on solriamfetol ([redacted], between-group least squares mean difference: [redacted], CS Section B.2.6.2.3.3).

In the open-label TONES 5 study,[redacted] in HRQoL measures (FOSQ-10, SF-36v2and ∆EQ-VAS) relative to baseline [redacted] (CS Section B.2.6.2.2.3). In response to clarification question A11 the company supplied graphs showing EQ-5D index scores and EQ-VAS scores from baseline to the end of the open label period [redacted] (also see section 4.2.7.1 of this report).

3.2.6.3 Subgroup 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 3 trial sub-group analyses. Results for TONES 4 and TONES 5 sub-group analyses are reported in CS sections B.2.7.2 and B.2.7.3 respectively. The ERG note that these analyses are under-powered to detect a statistically significant difference within and between sub-groups.

TONES 3

In TONES 3 the prespecified subgroups listed in CS Table 4 are compliance with OSA therapy, [redacted] and [redacted].

Compliance to OSA therapy

Although the rationale is not explicitly stated in the CS, it may be reasonable to presume that there could be a differential response between those compliant and non-compliant with primary OSA therapy, e.g. if non-compliant patients have a higher ESS at baseline, a greater response may be achieved. In response to clarification question A6, the company provided details of the baseline ESS scores in compliant and non-compliant patients in TONES 3. The ERG notes that across all study groups the baseline ESS score was higher in non-compliant patients (ranging from 15.8 to 16.6) than in compliant patients (ranging from 14.4 to 15.3).

Results from this sub-group analysis in TONES 3 are described in CS Section B.2.7.1 and CS Appendix E.1 and are summarised below in Table 21.

Table 21 Subgroup analysis in TONES 3: Compliance to OSA therapy

Outcome	Compliant N=241	Non-compliant N=103
LS mean difference (95% CI) in change from baseline ESS at week 12		
37.5 mg vs placebo	-2.4 (-4.2 to -0.5)	-0.7 (-3.5 to 2.1)
75 mg vs placebo	-1.3 (-3.1 to 0.5)	-2.6 (-5.4 to 0.1)
150 mg vs placebo	-4.2 (-5.7 to -2.7)	-5.0 (-7.2 to -2.9)
LS mean difference (95% CI) in change from baseline MWT at week 12 (minutes)		
37.5 mg vs placebo	4.81 (0.61 to 9.00)	3.70 (-1.97 to 9.36)
75 mg vs placebo	8.38 (4.30 to 12.47)	9.90 (4.44 to 15.36)
150 mg vs placebo	10.18 (6.78 to 13.58)	11.86 (7.46 to 16.26)
PGI-c, difference in % improved (95% CI) at week 12		
37.5 mg vs placebo	[redacted]	[redacted]
75 mg vs placebo	[redacted]	[redacted]
150 mg vs placebo	[redacted]	[redacted]

Source: CS Appendix E.1, Table 6, [redacted]

In summary:

- For ESS, a similar degree of improvement for the comparison between solriamfetol 150 mg and placebo was seen in the compliant and non-compliant subgroups (-4.2 and -5.0 respectively). The degree of improvement was not as similar for the compliant and non-compliant subgroups for the comparison between solriamfetol 75

mg (-1.3 and -2.6) and 37.5 mg doses (-2.4 and -0.7) and placebo, however this may reflect random variation because the numbers of patients were smaller in these groups (37.5 mg arm compliant n=39, non-compliant n=17; 75 mg arm compliant n=42, non-compliant n=16).

- Similar improvements in the change in MWT relative to placebo were seen for all solriamfetol doses in patients who were compliant/non-compliant with primary OSA therapy.
- Similar [redacted]

[redacted]

3.2.6.4 Safety outcomes

Adverse event data from the three TONES trials are summarised in CS Section B.2.10. [redacted]. The CS includes safety data for the unlicensed 300 mg solriamfetol dose as well as for the licensed doses (37.5 mg, 75 mg and 150 mg).

In the CSR for TONES 5 safety data specific to the open-label period only are presented stratified by modal dose (reflecting the dose patients took most frequently in the study) whereas summaries for the total TONES 5 period (open-label plus randomised withdrawal period) and for the randomised withdrawal period alone are presented by the actual dose taken at the time of the AE. The ERG notes that long-term safety data from TONES 5 for the licensed solriamfetol doses (75 mg and 150 mg only, the 37.5 mg dose was not included in TONES 5) in patients with OSA is limited because only [redacted] patients received a modal dose of 75 mg and [redacted] patients received a modal dose of 150 mg; the remainder ([redacted]) received the unlicensed 300 mg dose of solriamfetol. This reflects the study design, which titrated patients to the maximum tolerated dose of solriamfetol. Mean (SD) treatment exposure in the

OSA population was [redacted] ([redacted]) days ([redacted]) for all doses combined but less for the 75 mg dose ([redacted]) days) and 150 mg dose ([redacted] days).

Across all three trials, AEs were generally dose-dependent and non-serious (Table 22) A greater proportion of patients randomised to solriamfetol in TONES 3 had treatment-related AEs compared to placebo ([redacted]%) with [redacted] observed for 150 mg ([redacted]%) versus 75 mg ([redacted]%) and 37.5 mg ([redacted]%) during the first 12 weeks of treatment. The highest incidence of discontinuation due to AEs was reported in the longer-term TONES 5 study (8.6%; all doses combined; across the entire study, up to 52 weeks). In TONES 4, [redacted]% of patients experienced AEs during the titration phase (CS Table 22) declining to [redacted]% during the stable dose phase. Adverse event rates were higher in the patients in TONES 4 who were randomised to continue solriamfetol treatment ([redacted]%) compared with those who switched to placebo ([redacted]%).

Five patients in TONES 3 (1.2%, n=3 in solriamfetol licensed dose groups compared to 1.7%, n=2 in the placebo group) experienced serious AEs (Table 22); [redacted]. In TONES 5, 21 patients (all solriamfetol doses combined) experienced serious AEs, [redacted] of which occurred in licensed dose groups (75 mg or 150 mg). Of the 21 patients who [redacted] One death due to sepsis was reported in TONES 5 at the [redacted] and was considered unrelated to solriamfetol.

Table 22 Adverse events reported in TONES 3, TONES 4 and TONES 5 trials in OSA patients

Type of AE, n (%)	TONES 3 (Week 12)				TONES 4	TONES-5
	Placebo (N=119)	Sol 37.5 mg (N=58)	Sol 75 mg (N=62)	Sol 150 mg (N=117)	All doses combined (N=174)[a]	All doses combined (N=417)[b]
Any AE	57 (47.9)	37 (63.8)	30 (48.4)	83 (70.9)	[redacted]	313 (75.1)
Any treatment-related AE	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Serious AE	2 (1.7)	2 (3.4)	0	1 (0.9)	[redacted]	21 (5.0)
Any treatment-related serious AE	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
AEs leading to study/drug discontinuation	4 (3.4)	3 (5.2)	2 (3.2)	5 (4.3)	[redacted]	36 (8.6)
Deaths	0	0	0	0	[redacted]	1 (0.2)

Source: Compiled by the ERG from data presented in CS Tables 20-22 Sol: Solriamfetol
[a] Overall rates across all phases of the study (CSR Table 26). Event rates during the 2-week titration phase, stable dose phase and in the withdrawal phase are also reported separately (CS Table 22), these were more frequent in the initial titration phase.
[b] OSA sub-population.

CS Tables 20-22 present the most commonly reported AEs. The most frequently reported AE was headache in all three studies although the incidence varied from approximately 6.9% in those receiving the 37.5 mg dose in TONES 3 to 9.8% for all doses combined during the titration phase of TONES 4. Nausea, nasopharyngitis, anxiety, dry mouth and insomnia were also listed among the most frequent AEs in all three studies. The majority [redacted] of the most commonly reported events were mild or moderate in severity, dose-dependent and occurred in the first weeks after treatment started. AEs of special interest are discussed in Table 23.

Table 23 Adverse events of special interest

AE of interest	Concern	Main finding
Insomnia	Solriamfetol is a wake-promoting agent	• Insomnia events [redacted] with the exception of [redacted] (CSR Section 12.2.2.2). • In a small number of cases, insomnia led to study withdrawal (n=1 in TONES 3 in the 300 mg dose group, [redacted] in TONES 4 in the 150 mg group, CSR Section 12.3.3.3.3.2 and [redacted] in TONES 5, CSR Table 14.3.1.19.2).

AE of interest	Concern	Main finding
Depression & suicidal ideation	Depression is a common comorbidity in the target population with OSA.	• AEs associated with depression were reported [redacted] (CS Section B.2.10.3.2) in TONES 3 ([redacted]). No cases of treatment-emergent suicidal ideation were reported in TONES 3 in any solriamfetol group while two cases were reported in the placebo group. • In TONES 5 (CSR Table 14.3.1.19.2) [redacted] in the OSA sub-population ([redacted]% and [redacted]% in patients receiving solriamfetol 75 mg and 150 mg respectively) experienced an event classified within an event cluster defined as 'Depression and Suicidality'[a]). • Overall, there was no evidence to suggest an association between solriamfetol and an increased risk of suicidal ideation from the TONES trials.
Cardiovascular events, increased blood pressure[b] and increased heart rate	Patients with OSA may have comorbidities such as hypertension, obesity and diabetes which are major risk factors for cardiovascular events.	• In TONES 3, chest discomfort, palpitations, hypertension and increased blood pressure were reported in >1% of patients in the solriamfetol groups compared to 0% for placebo (CS Section B.2.10.3.3); No cardiovascular events were serious. Small dose-dependent changes in mean heart rate and blood pressure were observed in TONES 3 at week 12 (CS Table 23). • In the longer-term TONES 5 study the frequency of increased blood pressure was higher ([redacted]%[c]; all doses combined compared to 2.8% in TONES 3). • [redacted] serious cardiovascular events were observed in TONES 5 of which [redacted] occurred at the unlicensed 300 mg dose. [redacted] of the [redacted] serious events (i.e. cerebrovascular accident at the 150 mg dose and atrial fibrillation at the 300 mg dose) were considered related to study drug.

AE 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 or after 4 weeks treatment in TONES 4. • 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).[14]

[a] [redacted].

[b] [redacted]

[c] Source: CSR section 12.3.3.3.1.3

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. Precautions for use are recommended such as periodic monitoring of blood pressure and heart rate during treatment and control of pre-existing hypertension prior to starting solriamfetol.

3.2.6.5 Additional outcomes used in economic model

The economic model uses additional data form TONES 3 and TONES 5 to estimate discontinuation rates due to lack of efficacy.

In TONES 3, no patients were reported to have discontinued treatment due to lack of efficacy at week 12. Therefore, a discontinuation rate of [redacted]% due to lack of efficacy is assumed for the initiation phase of solriamfetol treatment in the company's base case economic model (CS section B.3.3.9).

In TONES 5, the discontinuation rate due to lack of efficacy for all three doses of solriamfetol combined was 3.6%. The company have subtracted the discontinuation rate due to lack of efficacy assumed in the initiation phase (0% during the first 12 weeks of treatment from TONES 3) from that observed in TONES 5 (3.6%) to provide an ongoing rate of

discontinuation due to lack of efficacy in the longer-term maintenance phase of treatment for the economic model.

3.2.6.6 ERG summary of clinical effectiveness results

- Efficacy data from the TONES trials suggest that solriamfetol reduces EDS in the short term starting from one week after initiation and that this effect is maintained over a longer period (up to 1 year). Efficacy was confirmed using a range of different outcome measures including the ESS, MWT and PGI-c.
- The effect of solriamfetol is dose-dependent with weaker effects on ESS scores observed at the lower doses of 37.5 mg and 75 mg where a clinically relevant difference relative to placebo was not observed (LS mean difference relative to placebo <2-3 points).
- There is some uncertainty over the best measure of treatment response for ESS. However, evidence of benefit compared to placebo was seen regardless of whether comparing LS mean change from baseline, the proportion of patients achieving a 3-point reduction in ESS score or the proportion of patients achieving normalisation of ESS score.
- The ERG notes that a strong placebo effect was observed with subjective outcome measures (ESS with PGI-c) but not when the more objective measure, MWT was used to measure response. The relevance of this finding remains unclear.
- Minimal changes in use of primary OSA therapy devices from baseline were seen during the TONES trials The ERG notes, however, that there are some uncertainties with respect to the sub-populations analysed, the impact of missing data and whether the lack of change observed in the clinical trial setting would be reflected in real world use.
- Solriamfetol had no material effect on generic measures of HRQoL (e.g. EQ-5D-5L) in the short or longer term. Statistically significant changes in the disease-specific measure FOSQ were observed in TONES 3 for the 150 mg solriamfetol dose only.
- Adverse events reported with solriamfetol in the TONES trials were generally dose-dependent and non-serious.

3.2.7 Pairwise meta-analysis of company study results

The company did not conduct meta-analysis given that there is only one known pivotal trial of solriamfetol in OSA (TONES 3).

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

The comparator to solriamfetol, as specified in the decision problem, is established clinical management (also referred to in the CS as standard of care / primary OSA therapy) without solriamfetol. The TONES 3 trial provided a head-to-head comparison of solriamfetol versus placebo, and in both trial arms patients were permitted to continue their primary OSA therapy (e.g. CPAP). Thus, the trial provides direct evidence of solriamfetol added to primary OSA therapy versus primary OSA therapy without solriamfetol (with the acknowledgement of a possibility of a placebo effect – which we discuss in more detail in section 4.2.6). Given the availability of a direct head-to-head clinical trial comparison between solriamfetol and primary OSA the CS did not include an indirect direct comparison. The ERG concurs that an indirect treatment comparison is not required for this appraisal.

3.4 Additional work on clinical effectiveness undertaken by the ERG

No additional work has been considered necessary by the ERG currently.

4 COST EFFECTIVENESS

The objective of the company's economic evaluation was to assess the cost effectiveness of solriamfetol for the management of EDS in patients with OSA, versus established clinical management without solriamfetol (see the company's decision problem, Table 3).

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

A systematic literature review (described in CS Appendix G) and an ad-hoc search conducted by the company did not identify any relevant economic evaluations or NICE technology appraisals that assessed interventions for EDS due to OSA. Only the NICE appraisal of CPAP for OSA, TA139, was deemed relevant.[15 16] This study was used by the company to inform various aspects of the economic model for the comparator of established clinical management without solriamfetol. An overview of the key assumptions of the economic analyses submitted for TA139 is presented in CS Table 24.

We note that interventions such as armodafinil, histamine H3 receptor inverse agonist MK-0249, dexamfetamine, modafinil and pitolisant can also be used for this indication but were not included in the systematic literature review. In response to Clarification Question B1, the company stated that neither MK-0249, pitolisant nor armodafinil are indicated for use in the OSA population in Europe, and based on KOL Interviews, there is no evidence to suggest these treatments are used in England for EDS due to OSA. The company conducted a new search combining the original disease and study design terms with the intervention terms for pitolisant, armodafinil and MK-0249; this search found no relevant references that would have informed the analysis (see Response to Clarification Question B1).

ERG conclusion on cost-effectiveness search

We consider the company's search strategy for published cost-effectiveness studies to be thorough, so it is not likely that relevant studies would have been missed.

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

4.2.1 NICE reference case checklist

The ERG assessment of whether the company's economic evaluation meets NICE Reference Case requirements is presented in Table 24.

Table 24 NICE reference case checklist

Element of assessment	Reference case	ERG comment on company's submission
Perspective on outcomes	All direct health effects, whether for patients or, when relevant, carers	Yes, only direct health effects are included in the company's base case. The impact of the partner utility on the economic outcomes is assessed in a scenario analysis. It is debateable whether this should be included, as partners are not necessarily carers.
Perspective on costs	NHS and PSS	Yes
Type of economic evaluation	Cost–utility analysis with fully incremental analysis	The company present a cost–utility analysis.
Time horizon	Long enough to reflect all important differences in costs or outcomes between the technologies being compared	Yes, a lifetime time horizon in the base case and shorter periods (5, 10...50 years) in scenario analyses.
Synthesis of evidence on health effects	Based on systematic review	No. Solriamfetol is a new treatment, and the clinical evidence for solriamfetol in the management of EDS due to OSA comprises the solriamfetol clinical trial programme (sponsored by Jazz Pharmaceuticals) used to support solriamfetol marketing authorisation application. In addition, there are no active pharmacological treatments within the company decision problem. Therefore, a clinical effectiveness systematic literature review has not been conducted.
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.	The model outputs include QALYs. In the company's base case, utilities are derived from a mapping from ESS to EQ-5D (see section 4.2.7.3 below). The company does not use EQ-5D data from the TONES 3 trial in their economic analysis (CS B.3.4).
Source of data for measurement of health-related quality of life	Reported directly by patients and/or carers	EQ-5D data for the mapping in the company's base case was obtained from an online survey of people with self-reported OSA (CS B.3.4.2.2). EQ-5D data from patients in the TONES 3 trial was not used in the economic analysis.
Source of preference data for valuation of changes in health-related quality of life	Representative sample of the UK population	The mapping study used in the company's base case uses EQ-5D-5L data valued using the van Hout cross-walk algorithm, as recommended by NICE.[17] However, it is not stated whether the UK value set is used. The method for valuing EQ-5D-5L data for the TONES 3 and TONES 5 studies is not specified in the CS or trial reports.

Element of assessment	Reference case	ERG comment on company's submission
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	The cost of established clinical management for OSA is excluded from the company's analysis because the addition of solriamfetol to standard OSA therapy is expected to have no impact on the delivery of standard care.
Discounting	The same annual rate for both costs and health effects (currently 3.5%)	Yes
EQ-5D, standardised instrument for use as a measure of health outcome; PSS, personal social services; QALYs, quality-adjusted life years.		

4.2.2 Model structure

The company's model builds on the model structure used in the TA139 NICE appraisal of CPAP for OSA.[16]. For a brief description of the TA139 Assessment Group's model please refer to CS section B.3.2.

The company use a two-stage model composed of a decision tree (Figure 2), which reflects the first 12 weeks of treatment, and a Markov model (Figure 3), with annual cycles and half-cycle correction, used for the remainder of the model time horizon. The Markov model has three health states: **Responders, Non-responders and Dead.** It estimates life years (LYs), quality-adjusted life years (QALYs) and direct costs from the NHS and Personal Social Services (PSS) perspective. It was developed in Microsoft® Excel 2016.

In the model, response status is assessed at 12 weeks after treatment initiation, based on the change in ESS from baseline. Response is defined by an absolute reduction of at least 3 points from baseline ESS (as described in section 4.2.6.1 and CS section B.3.3.3). Rates of response are estimated using 'centred' ESS scores (as explained in CS section B.3.3.2 and section 4.2.6.1 below). This centring approach essentially assumes that the improvement in ESS observed in the TONES 3 placebo arm is entirely due to a 'Hawthorne effect' and would not occur in clinical practice. Mean ESS for patients in the 'standard care' arm in the model is therefore assumed to be constant, and ESS changes for patients in the solriamfetol study arms are adjusted to model the ESS improvements relative to the placebo arm.

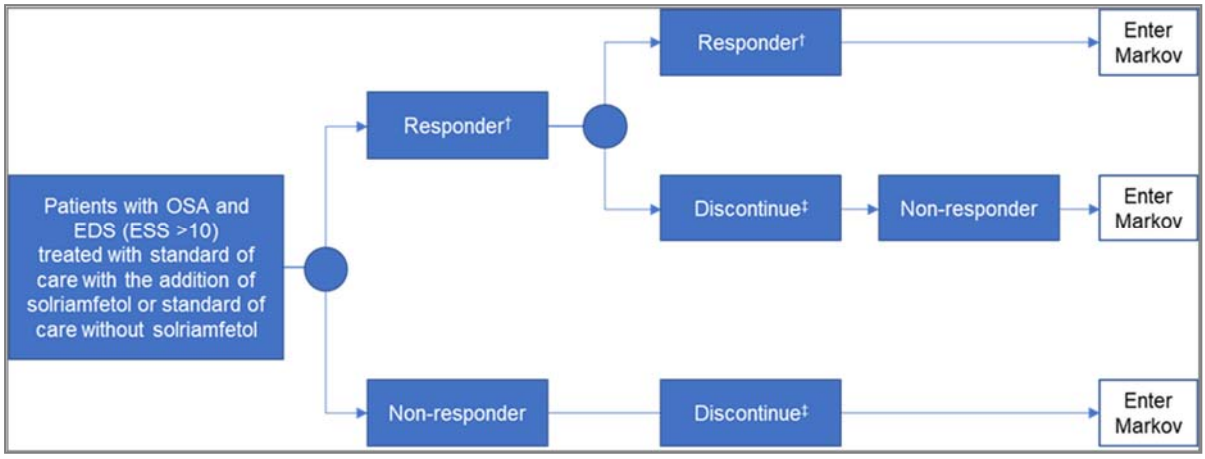


Figure 2 Treatment initiation (first 12 weeks) – Decision tree

Source: CS Figure 16
Abbreviations: EDS, excessive sleep disorder; ESS, Epworth Sleepiness Scale.
† A responder was defined as a patient achieving a reduction in ESS ≥3. ‡ Patients discontinued solriamfetol treatment but continued standard care for the lifetime of the model.

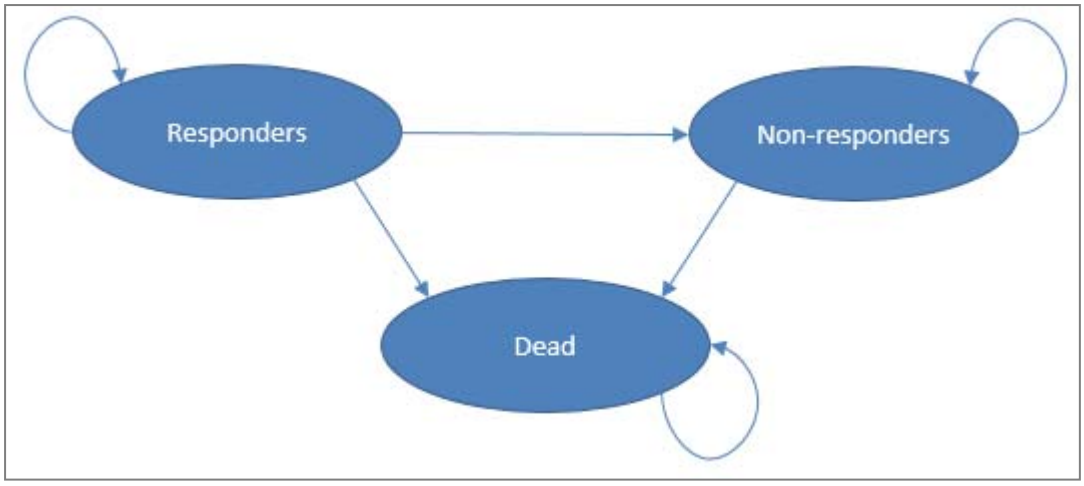


Figure 3 Maintenance treatment (12 weeks onward) – Markov model

Source: CS Figure 17

People whose disease has not responded to solriamfetol by 12 weeks are defined as *Non-responders* and assumed to stop solriamfetol. On treatment cessation, ESS is assumed to return to the mean baseline value ($ESS_{baseline}$) for the included population: 15.6 for patients with baseline ESS>10 in the TONES 3 mITT, as defined in section 3.2.3.1 above (see Table 25 and CS Table 25). We note that TONES 3 patients with baseline ESS=10 are excluded from the economic analysis.

People identified as responders at the 12-week assessment move into the *Responders* health state, continue to receive the same dose of solriamfetol and maintain their 12-week ESS reduction unless they discontinue treatment due to loss of response or adverse event

(section 4.2.6.4). As for non-responders, it is assumed that ESS for patients who discontinue solriamfetol returns immediately to $ESS_{baseline}$.

It is assumed that all patients remain on the standard OSA therapy regardless of their treatment response status for the duration of the simulation (CS section B.3.3.7).

Utility values, stratified by treatment and response status, are estimated from the $ESS_{baseline}$ and the mean change in ESS from baseline at the point of response assessment. The utility estimates are shown in CS Table 31 (further details are provided in section 4.2.7 below).

Improvement in ESS and the associated impact on HRQoL are assumed to occur one week after treatment initiation (CS Figure 5) in all patients regardless of their treatment response status, i.e. non-responders are also assumed to have treatment response up to the point of response assessment. The impact of the latter assumption is tested in a scenario analysis.

The model incorporates age- and gender-specific general population mortality (based on the Office of National Statistics life tables)[18] because addition of solriamfetol to standard care is assumed to have no impact on patients' survival (see CS section B.3.3.10). When discussing the increase in the risk of cardiovascular complications and stroke (CS page 126), the company states that relative changes in systolic blood pressure in the TONES trials were small and, therefore, this risk is not modelled. Road traffic accidents are also excluded from the model because "in the UK, for patients with EDS due to moderate to severe OSA, or for patients with EDS due to mild or suspected OSA whose symptoms are uncontrolled after a period of ≥3 months, their OSA is considered a 'notifiable' medical condition by the DVLA, and they must surrender their driving licence" (CS page 125).

ERG conclusion on model structure

The structure of the company's model, with three health states (responder, non-responder and dead), is appropriate for the decision problem, given their 'centring' adjustment of ESS results from the TONES 3 trial. This adjustment assumes that the observed ESS improvement in the TONES 3 placebo arm would not occur in practice and estimates ESS changes with solriamfetol relative to a flat ESS for standard care. This removes any need to model the impact of standard care after the 12-week assessment.

However, we question whether the centring approach is appropriate, as it assumes away improvements in the placebo arm of the trial, which could, at least in part, be

due to a natural ‘regression to the mean’ effect (see CS B.3.3.2 and 4.2.6 below). When unadjusted ESS scores are used in the model, the 3-state structure cannot adequately reflect changes over time for patients who discontinue solriamfetol but retain some ESS improvement compared with baseline (as for patients in the standard care arm who never commenced solriamfetol treatment. We therefore amend the model structure for our analyses with unadjusted TONES 3 ESS IPD (see section 4.2.3 below). We add a fourth health state for patients who discontinue solriamfetol due to AEs, a proportion of whom retain an ESS response (see illustrated in Figure 12 to Figure 14 below).

We also note that some features of the model may not reflect clinical practice. In the model, ‘response’ and treatment continuation is entirely based on a reduction in ESS score from baseline. In clinical practice, other factors, including the impact of treatment on patient’s quality of life, may also be considered when assessing patient’s response to treatment.

The timing of response assessment may differ from the 12 weeks assumed in the model (as in the TONES 3 trial). Clinical advice suggests that assessment of response is currently conducted from 6 weeks to 3 months from treatment initiation. In the company’s model, the response assessment is modelled at 12 weeks (as in the TONES 3 trial). We adopt the company’s assumption in our base case and conduct a scenario for the point of response assessment at week 8 using TONES 3 IPD.

The impact of OSA and EDS on cardiovascular risk is not modelled. Our clinical experts confirmed that the change in systolic blood pressure in the TONES 3 trial was minimal. We note that excluding the effect of CPAP on cardiovascular events in TA139 did not lead to significant changes in the cost-effectiveness results.

4.2.3 Population

The modelled population comprises adults with EDS due to OSA who have an ESS score of >10 at baseline. Characteristics of the modelled population were based on those for the TONES 3 mITT population with baseline ESS>10: mean age [redacted] years, 37.7% female.

4.2.3.1 Baseline EDS severity

Mean baseline ESS is also based on the TONES 3 population. On request from the ERG, the company provided unadjusted individual patient data (IPD) for the mITT population from TONES 3, which was used in the company's model. Mean ESS at baseline, 1, 4, 8 and 12 weeks, estimated from the IPD is shown in Table 25. The mean change from baseline to 12 weeks from IPD are similar, but not identical, to the aggregate trial results. This is due to the method of analysis for the primary trial outcomes, which include adjustment for stratification by baseline compliance with OSA therapy (see Table 11 above).

Table 25 Mean ESS scores estimated from TONES 3 IPD (mITT population)

Treatment arm	N	Base-line	Week 1	Week 4	Week 8	Week 12	Mean change (0 to 12 weeks)
Placebo	114	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Solriamfetol 37.5 mg	56	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Solriamfetol 75 mg	58	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Solriamfetol 150 mg	116	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Source: Estimated by the ERG from IPD for the TONES 3 mITT population

Mean baseline ESS in the company's economic model was [redacted], based on a sub-group of the TONES 3 population, with baseline ESS restricted to >10. We show mean ESS from baseline to week 12 in the whole mITT TONES 3 population (Figure 4) and in the sub-group with ESS>10 at baseline (Figure 5). Reductions are slightly larger in the >10 ESS subgroup. The relationship between baseline ESS and 12-week ESS reduction is also illustrated in Figure 6, which shows a positive correlation based on TONES 3 IPD for 75 mg solriamfetol.

Figure 4 Mean ESS 0 to 12 weeks: TONES 3 mITT population (baseline ESS≥10)

Source: prepared by the ERG using IPD from TONES 3

Figure 5 Mean ESS 0 to 12 weeks: TONES 3 mITT population (baseline ESS>10)

Source: prepared by the ERG using IPD from TONES 3

Figure 6 Relationship between baseline ESS and mean ESS reduction

Source: prepared by the ERG using IPD from TONES 3

4.2.3.2 Compliance with primary OSA therapy

Results of the sub-group analysis for compliance with primary OSA therapy (see section 3.2.6.3 above) suggest that solriamfetol is more cost-effective for the non-compliant sub-group, with the ICER for the compliant sub-group exceeding the £30,000 per QALY threshold (see CS section B.3.9.1, and section 5.2.3 below).

ERG conclusion on model population

Expert clinical advice suggests that the demographic characteristics of patients in the TONES 3 trial and economic model are reflective of patients with OSA whose EDS has not been satisfactorily treated by a primary OSA therapy.

However, our experts and members of the company's Scottish Advisory Board, noted that the mean baseline ESS score in the TONES 3 trial (around 15) is higher than would be routinely observed in clinical practice.

Mean baseline ESS score in the company's base case economic model (15.55) is increased by the use of IPD for people with ESS>10 (rather than ESS≥10 as in TONES 3). The company argues that this is "broadly consistent" with the marketing

authorisation for solriamfetol which defined the presence of EDS from ESS≥10. We believe that for the main analysis ESS ≥10 would be more appropriate. Restriction to a population with ESS>10 is likely to increase effectiveness, and hence the cost-effectiveness of solriamfetol. However, this increases uncertainty by reducing the sample size on which the analysis is based.

In TONES 3, 73.5% of patients receiving solriamfetol self-reported current or prior primary OSA therapy use, and of this proportion 92.7% of patients had used or were using PAP at baseline. Compliance with primary OSA therapy was around 70% in solriamfetol patients at baseline. As discussed earlier, expert clinical opinion suggests this estimate is higher than usually seen in practice.

The company conduct subgroup analysis for people who were or were not compliant with PAP at baseline in TONES 3. Long-term compliance with CPAP is variable, and studies quote non-compliance rates as high as 50% in the first year (see CS Sleep Services Market Research Supplement, and section 3.2.6.3 above). We conduct a subgroup analysis using the raw (unadjusted) IPD, and we also estimate an ICER assuming that 50% of patients are not compliant at baseline (see section 6).
In addition to the question of baseline CPAP compliance, there is uncertainty over potential changes in CPAP compliance over time associated with the use of solriamfetol. The company reported an exploratory analysis that showed that changes in use of primary OSA therapy in TONES 3 were small and similar between solriamfetol and placebo arms (CS B.2.6.1.8). See section 3.2.6.1.4 above for ERG critique of this analysis.

4.2.4 Interventions and comparators

The intervention in the company's analysis is solriamfetol in addition to established clinical management (as described in section 2.2.3 above). The analysis is conducted for solriamfetol doses of 37.5 mg, 75 mg and 150 mg in accordance with the EMA marketing authorisation (CS Appendix C); the 300 mg dose is unlicensed and is, therefore, excluded from the company's analysis. A potentially important question for the economic analysis is the proportion of these three doses that are would be used in clinical practice: this affects the treatment cost as well as effectiveness and adverse event parameters in the model. We discuss the solriamfetol dose split in section 4.2.8.1.2 below.

The CS states (page 135) that “solriamfetol represents the only licensed treatment option for the management of EDS in patients with OSA whose EDS has not been satisfactorily treated by a primary OSA therapy”. Therefore, the only comparator considered in the analysis is established clinical management without solriamfetol, as per the company’s decision problem (see Table 3 above). Expert clinical advice to the ERG is that residual EDS in OSA is sometimes treated with off-label drugs, including modafinil. However, only a minority of patients are likely to receive this, and it cannot be considered standard practice.

4.2.5 Perspective, time horizon and discounting

The company’s base case takes the perspective of the NHS and PSS in England. Both cost and outcomes (LYs and QALYs) are discounted at 3.5%, in line with the NICE guidance.[19] The impact of discounting at 0% and 6% is assessed in scenario analyses.

4.2.6 Treatment effectiveness and extrapolation

4.2.6.1 Change from baseline ESS and treatment response

The company models the response to treatment with solriamfetol based on the change in ESS from baseline estimated at week 12. The mean change in ESS in the mITT population from the pivotal TONES 3 trial is shown in CS Table 13 and Table 12 above. However, in the model, the change in ESS from baseline and the difference in change from baseline for solriamfetol versus placebo are estimated from TONES 3 IPD. As noted in section 4.2.3, the mean IPD results that drive the model are not the same as the LS regression estimates for clinical outcomes from the trial (see Table 26 below). This is because the latter were adjusted for baseline compliance with primary OSA therapy, a stratification factor in the trial’s randomisation of participants (see Table 11). In addition, the company’s base case economic analysis is restricted to a subgroup of IPD for patients with ESS>10 at baseline, rather than the TONES 3 mITT population.

The rationale for the use of IPD rather than aggregate data in the model is to allow changes in ESS to be dichotomised in terms of response/non-response. In turn, this enables modelling of the 12-week assessment and discontinuation of treatment for ‘non-responders’ and the risk of loss of response and treatment discontinuation for initial responders in subsequent model cycles. The IPD enables estimation of both the initial proportions of responders and the mean ESS (and hence utility) for responders and non-responders. This process of dichotomisation is explained in CS section B.3.3.3 and Figure 18. CS Table 28 shows the company’s base case estimates of the proportions of responders at 12-week

assessment and mean ESS for responders and non-responders, calculated from the IPD. Note that the company assumes that the proportion of responders under standard care is zero, which does not reflect the observed reduction in ESS in the TONES 3 trial (see CS Figure 5). This results from a 'centring' adjustment, as explained below.

Table 26 Comparison of TONES 3 ESS effects from main analysis and IPD (mITT)

Change in mean ESS from baseline to week 12 (ΔESS)	Placebo	Solriamfetol 37.5 mg	Solriamfetol 75 mg	Solriamfetol 150 mg
Co-primary analysis (MMRM)				
Number of patients	114	56	58	116
ΔESS	-3.3	-5.1	-5.0	-7.7
ΔESS difference relative to placebo	-	-1.9	-1.7	-4.5
Proportion of responders (ΔESS ≥3)	[redacted]	[redacted]	[redacted]	[redacted]
IPD analysis				
Number of patients	114	56	58	116
ΔESS	[redacted]	[redacted]	[redacted]	[redacted]
ΔESS difference relative to placebo	-	[redacted]	[redacted]	[redacted]
Proportion of responders (ΔESS ≥3)	[redacted]	[redacted]	[redacted]	[redacted]
Mean ESS for responders	[redacted]	[redacted]	[redacted]	[redacted]
Mean ESS for non-responders	[redacted]	[redacted]	[redacted]	[redacted]
IPD analysis with centring				
ΔESS difference relative to placebo	-	[redacted]	[redacted]	[redacted]
Proportion of responders (ΔESS ≥3)	[redacted]	[redacted]	[redacted]	[redacted]
Mean ESS for responders	[redacted]	[redacted]	[redacted]	[redacted]
Mean ESS for non-responders	[redacted]	[redacted]	[redacted]	[redacted]
IPD analysis ESS>10				
Number of patients	109	53	55	107
ΔESS	[redacted]	[redacted]	[redacted]	[redacted]
ΔESS difference relative to placebo	-	[redacted]	[redacted]	[redacted]
Proportion of responders (ΔESS ≥3)	[redacted]	[redacted]	[redacted]	[redacted]
Mean ESS for responders	[redacted]	[redacted]	[redacted]	[redacted]
Mean ESS for non-responders	[redacted]	[redacted]	[redacted]	[redacted]
IPD analysis with centring ESS>10 (company base case)				
ΔESS difference relative to placebo	-	[redacted]	[redacted]	[redacted]
Proportion of responders (ΔESS ≥3)	[redacted]	[redacted]	[redacted]	[redacted]
Mean ESS for responders	[redacted]	[redacted]	[redacted]	[redacted]
Mean ESS for non-responders	[redacted]	[redacted]	[redacted]	[redacted]

Source: Co-primary analysis (MMRM) from CS Table 13 and company response to clarification question A8: other results calculated by the ERG from the revised version of the company model and IPD submitted with the company's response to clarification questions.

4.2.6.2 Adjustment for placebo-arm response ('centring')

The company argues that the reduction in ESS observed in the placebo arm of TONES 3 would not occur outside the context of a clinical trial for patients continuing 'standard care', without addition of an active treatment. They present a detailed discussion of possible explanations for the placebo arm ESS changes in CS sections B.3.3.2 and B.3.3.3, suggesting three potential mechanisms for these effects:

1. "**Regression to the mean**", which occurs when there is natural variation over time in the severity of a condition and when people are more likely to be recruited to a clinical trial during a bad phase of the condition. In this case, one would expect a natural improvement during follow up for all treatment arms, both within the clinical trial and in routine practice.
2. "**Hawthorne effect**", where the process of observation encourages patients to expect an improvement, which may be translated to an observed improvement, particularly with subjective outcome measures (such as the ESS). This effect would lead to better outcome measures across all treatment arms within a trial, but the improvement would not occur in routine practice. Thus, the relative difference between active and placebo arms from the trial would be maintained in practice.
3. "**True placebo**", which is caused by patient expectations related to the process of active or placebo treatment. This effect would continue in the real world for an active treatment, but not for standard care without placebo.

Importantly, these mechanisms have different implications for transferability of trial results to routine practice. With regression to the mean, the absolute trial effects would be maintained. With Hawthorne effects the absolute effects would be reduced but the relative effects maintained. With a true placebo, the relative difference between the active treatment and standard care would be increased.

The company argues that regression to the mean is not a likely explanation for the placebo arm improvement in TONES 3. They put forward four arguments to support this assertion:

i) The magnitude of the ESS improvement;
ii) The stability of MWT results for the placebo arm across all timepoints;
iii) The stable use of primary OSA in TONES 3 patients at baseline; and
iv) Changes over time for patients withdrawn from treatment in the TONES 4 trial who subsequently restarted treatment in the TONES 5 maintenance trial.

We suggest that of these arguments, the MWT results present the strongest evidence against 'regression to the mean'. MWT is a more objective test than ESS, and there are

clear differences in changes over time in the TONES 3 placebo arm between ESS (CS Figure 5) and MWT (CS Figure 6): MWT does not change through the 12-week follow up; whereas ESS falls in week 1 and maintains this reduction through to week 12.

We note however, that MWT and ESS do measure different (though obviously related) concepts. ESS measures EDS (likelihood of dozing) in different day to day contexts, recalled over a [redacted] period by patient self-report. MWT measures patients' ability to remain awake (sleep latency/ wakefulness) over a pre-defined period of minutes, repeated a set number of times in a day, in a sleep laboratory. It is possible that the MWT may be stable over time, while ESS is more volatile. If so, and if patients are more likely to seek clinical help, and hence more likely to be entered into a clinical trial, when they are experiencing subjective problems with daytime sleepiness as reflected in the ESS, then regression to the mean is still a possibility for ESS even if it is not for MWT.

Of the remaining potential placebo mechanisms, the company choose to assume a Hawthorne effect for their base case, as this is more conservative than the true placebo explanation. They therefore conduct a "centring" exercise to adjust the IPD results for both the solriamfetol and placebo arms, following the approach proposed by Hawkins 2010.[20] This entails assuming that all patients treated with standard care would remain at their baseline ESS for the duration of the model, while each individual ESS record in the IPD of the solriamfetol arms is adjusted by subtracting the mean change from baseline ESS (∆ESS) for the respective timepoint in the placebo arm. (Note this is not the same as simply subtracting the mean baseline ESS of the placebo arm from each solriamfetol observation, as described on page 140 of the CS). The centring exercise thus adjusts the change from baseline to week 12 in the solriamfetol arms by the mean observed change from baseline to week 12 in the placebo arm. The modelled mean ESS for responders and non-responders, together with response rates for different treatment arms, are shown in CS Table 28.

ERG conclusion on placebo-arm adjustment

The company's description of the centring exercise is incorrect, but we were able to verify centred ESS scores using raw IPD: we subtracted the mean ∆ESS in patients on standard care from ∆ESS for each individual patient from the solriamfetol treatment arms as described in Hawkins 2010.[21]

The centring of the IPD is the most influential model assumption. The company provides a good discussion of alternative explanations for the ESS improvement observed in the placebo arm of the TONES 3 trial (CS B.3.3.2). The use of

unadjusted effects on ESS for all trial arms to represent expected outcomes in clinical practice (including use of placebo results to model real-world standard care outcomes) relies on an assumption that the change in the placebo arm is entirely due to regression to the mean, that would occur equally with standard care and solriamfetol add-on therapy.

The company present several arguments against regression to the mean. We note in particular their argument that the lack of placebo arm improvement for the less subjective co-primary outcome of MWT (CS Figure 6) lends support to the assumption that the placebo arm improvement for ESS (CS Figure 5) would also not be fully explained by a 'regression to the mean' effect. This may be true, although it does not necessarily follow. It is possible that sleep latency may be stable over time while daytime sleepiness is more variable. If so, regression to the mean is still a possibility for ESS even if not for MWT.

There is no direct evidence for the relative effect of solriamfetol add-on therapy compared with standard care alone (i.e. without placebo) to validate the centring approach. Therefore, in the ERG base case, we prefer to use unadjusted (non-centred) trial data (i.e. based on the observed placebo arm results), and we conduct a scenario with the centred IPD. We describe our non-centred version of the model in section 6 below. This allows for a proportion of patients treated with standard care alone to experience an improvement in ESS sufficient for them to meet the response definition. Thus, mean ESS can change over time in both standard care and solriamfetol treatment arms.

We follow the company's assumption that standard OSA therapy is continued in all patients throughout simulation, with or without add-on solriamfetol treatment. This simplified assumption is made because of the lack of long-term evidence on discontinuation of standard care for OSA in patients with residual EDS, which is a limitation of this economic analysis.

4.2.6.3 Definition of treatment response

In the company's base case, response is defined as at least a 3-point reduction in ESS from baseline; the reduction in ESS of ≥2 and ≥4 points is assessed in scenario analyses.

According to CS Key Opinion Leaders (KOL) Clinical Practice Interviews (which the company refer to as ""UK KOL Evidence", see CS page 18), there is considerable variation in how response to treatment of EDS is defined in clinical practice, from the reduction in ESS

of 2-3 points to normalisation in the ESS score. This has also been confirmed by our clinical experts.

In the ERG base case, we define the response as a reduction in ESS of at least 2 points, following expert advice. We also conduct scenarios for treatment response defined as (1) a change in ESS of at least 3 points (the company's base-case assumption) (see section 6), and (2) a change in ESS of at least 4 points.

4.2.6.4 Treatment discontinuation

Treatment discontinuation due to loss of response and AEs in the pivotal TONES trials is discussed in sections 3.2.4.3 and 3.2.4.4 above.

4.2.6.4.1 Discontinuation due to AEs

The observed rate of AEs in TONES 5 was dose dependent, but the company's analysis assumes the same annual rate of TEAE related discontinuations of 3.7% for all doses of solriamfetol in both treatment initiation and maintenance phases (for a detailed argument see CS section B.3.3.8). The company wrote (CS page 147): "As patients in the standard care only arm of TONES 3 were not receiving active treatment, this is assumed for the solriamfetol arms only." NB: In the company's model, the discontinuation rate of 3.7% per year is also applied to the standard care arm from year 2 onwards (see section 5.3.1).

4.2.6.4.2 Discontinuation due to loss of response

As for the treatment discontinuation due to AEs, the observed discontinuation due to loss of response to solriamfetol was also dose-dependent, but the same rate of 3.6% is applied in the first and consecutive years across the solriamfetol treatment arms (CS section B.3.3.9).

ERG conclusion on treatment discontinuation

The company reports that treatment discontinuation due to AEs and loss of response in the TONES trials was dose-dependent (CS B.3.3.8), but the modelled rates in the company base case are the same across all solriamfetol doses. In our base case we apply dose-dependent discontinuation rates due to AEs and loss of response, estimated from TONES 5 (shown in Appendix 9.1).

The company's model, with 'centring' assumptions, does not allow for response in the standard care arm. However, in our version of the model we assume that ESS can vary with standard care and that a 'response' is possible without solriamfetol treatment. The loss of response rate in the standard care arm is highly uncertain. For

the standard care arm, we take a weighted average of discontinuation rates from the solriamfetol treatment arms (the rationale is explained in Appendix 9.1).

4.2.6.5 Bootstrapping for estimation of treatment effect

The CS states (CS section B.3.7) that because of the relatively small sample size for each solriamfetol dose in TONES 3, the company use bootstrapping of IPD to model uncertainty over response rates and mean ESS with/without response. This method is employed in a scenario analysis for the company's base case as described below: a sample of 5,000 patients is drawn, with replacement, from the mITT population for each treatment arm, and the associated costs and quality-adjusted life-years (QALYs) are recorded for each treatment; the resampling process is repeated 1,000 times; and the costs and QALYs are averaged and used for the estimation of the incremental cost effectiveness ratio (ICER).

The same bootstrapping method is also applied in the company's probabilistic sensitivity analysis (PSA), with the only difference being that the sample size in this analysis is arm-specific and equal to the number of patients in the corresponding treatment arm in TONES 3.

ERG conclusion on the use of bootstrapping

We believe that it is appropriate to use bootstrapping in the PSA to represent uncertainty around the effectiveness parameters in the model: proportion of responders and mean change in ESS for responders and non-responders. This is because these three input parameters are correlated, and the distributions of the change in ESS from baseline are skewed (see Appendix 9.3).[21]

However, the size of the bootstrapped sample for each treatment arm should have been the same as that of the original dataset in both the PSA and the base-case analysis.[22] We correct this in our analysis (see section 6).

In addition to their base-case results (which are deterministic), the company present results with 'the bootstrapping method' (CS Table 36). This accounts for uncertainty around and correlations between the three effectiveness input parameters. However, it does not allow for interactions between these and other uncertain model parameters (such as utilities). We, therefore, consider that the full PSA results provide the best estimates of cost-effectiveness and we use these in the ERG analyses (section 6).

4.2.7 Health state utilities

4.2.7.1 EQ-5D utility estimates from TONES 3

EQ-5D data is collected in the TONES 3 trial but not used to inform utility estimates in the company's economic model (CS B.3.4).

Patients randomised in TONES 3 were asked to complete the EQ-5D-5L questionnaire at baseline, 1, 4, 8 and 12 weeks, and then after a further 14, 27 and 40 weeks (26, 39 and 52 weeks from original baseline) of open-label solriamfetol treatment in TONES 5 (Group A). Patients initiated on solriamfetol in TONES 5 (Group B) were also followed up for 52 weeks in total. The CS and reports of the TONES 3 and 5 do not state how the EQ-5D-5L Index scores were calculated.[23-25] Therefore, it is not clear whether reported TONES EQ-5D-5L Index results meet NICE Reference Case requirements.[19]

We summarise results from health-related quality of life outcomes in Tones 3 and 5 studies in section 3.2.4.2 above. Mean baseline EQ-5D Index (utility) scores in TONES 3 (mITT population) were [redacted] in the placebo arm and [redacted] in the solriamfetol arms (CS B.2.6.1.10), similar to estimates for people of similar age (55 years) in the general population: 0.86 for men and 0.84 for women.[26] There were no significant effects on EQ-5D-5L Index scores.

In response to clarification question A10, the company provided graphs to show how measures of health-related quality of life changed from baseline to 12 weeks in the TONES 3 trial (Clarification response Figures 1 to 5). We reproduce these graphs for the FOS-Q overall score, SF-36 Physical Component Score (PCS) and Mental Component Score (MCS) and the EQ-5D Index score in Figure 7 to Figure 10 below. These show broadly similar trends for the FOS-Q, SF-36 PCS and MCS, with improvements in the first week for all arms (including placebo) which are maintained at 12 weeks, although mean differences versus placebo were only significant for the solriamfetol 150 mg dose (CS Table 14). In contrast, the EQ-5D Index score improved across all arms in the first week, but there were no consistent trends over 12 weeks.

TONES 5 showed small non-significant improvements in all quality-of-life measures, including the EQ-5D, for patients on open label solriamfetol over one year of follow up (CS Figures 10 and 11 and Clarification response Figures 6 to 13).

The company argue that the lack of a significant effect for EQ-5D in TONES 3 is inconsistent with the other outcome measures in the trial and with evidence from the literature. They put forward various hypotheses that may explain this 'anomaly' in CS section B.3.4:

- The lack of domains related to sleepiness or relationships, which are known to be associated with OSA and EDS.
- A ceiling effect, as high baseline scores left little room for improvement. This is illustrated with a comparison of baseline EDS severity and improvements with treatment for people with a high baseline EQ-5D score (0.9 or higher) compared with this with a lower baseline EQ-5D (less than 0.9) (CS Table 29).
- It is suggested that the lack of change in EQ-5D Index scores may be explained as patients with a long-standing condition such as OSA with EDS adapting their expectations of what activities are normal and how they should feel.

Figure 7 LS mean (SE) change from baseline in FOSQ-10 total score (TONES 3)

Source: Reproduced from clarification response Figure 1
FOSQ-10, Functional Outcomes of Sleep Questionnaire; LS, least squares; SE, standard error. * $p<0.05$; † $p<0.01$ vs placebo

Figure 8 LS mean (SE) change from baseline in SF-36 PCS scores (TONES 3)

Source: Reproduced from clarification response Figure 2

LS, least squares; PCS, physical component summary; SE, standard error; SF-36, Short Form 36 Health Survey. * p<0.05; † p<0.01 vs placebo

Figure 9 LS mean (SE) change from baseline in SF-36 MCS scores (TONES 3)

Source: Reproduced from clarification response Figure 3

LS, least squares; MCS, mental component summary; SE, standard error; SF-36, Short Form 36 Health Survey. * p<0.05; † p<0.01 vs placebo

Figure 10 LS mean (SE) change from baseline in EQ-5D Index scores (TONES 3)

Source: Reproduced from clarification response Figure 5

LS, least squares; EQ-5D, EuroQol Health Questionnaire; SE, standard error. Note that where multiple arms had the same EQ-5D Index value, the legend symbol is presented next to its LS mean (SE).

4.2.7.2 Evidence from the literature on utilities

4.2.7.2.1 EQ-5D utilities for OSA with EDS

The company conducted a systematic literature review to identify other sources of utilities for people with EDS caused by OSA (CS Section 3.4.1 and Appendix H). The ERG had no concerns over the conduct of the search, although as it was last updated in February 2020, we ran another update to identify any relevant recent publications.

The company identified 33 studies, of which five met the NICE reference case.[19] These references differ from those reported in the CS because we consider that the 1997 and 1998 papers by Jenkinson et al. relate to the same dataset and that the PREDICT trial reported by McMillan et al. meets the NICE reference case.[19] We summarise the results of the five reference case studies in Table 27 below. Two out of three studies that reported mean EQ-5D Index values before and after use of CPAP found a statistically significant change. Two NIHR HTA funded UK RCTs, PREDICT and TOMADO, found small non-statistically significant effects with the EQ-5D for CPAP and mandibular devices, respectively.

As in TONES 3, Jenkinson et al. reported that the SF-36 PCS and MCS measures of quality of life were more sensitive to change in EDS than the EQ-5D.[27 28] The large UK PREDICT trial also found a larger mean QALY difference between CPAP and best supportive care based on the SF-6D than with the EQ-5D: 0.018 (95% CI: 0.003 to 0.034) compared with 0.005 (95% CI: –0.034 to 0.044).[29 30]

Table 27 Utility estimates from literature: EQ-5D meeting NICE reference case requirements

Study, country	Population	Mean age (% male)	Study design	Health states	Sample	ESS mean	Utility mean	Comments
						Before/ after		
Jenkinson 1997 & 1998, UK[27 28]	OSA 79% with ESS>9	50 years (100%)	Observational (before/after)	CPAP	108	14/ 8	0.79/ 0.84	• EQ-5D-3L UK value set • Authors report larger effect sizes for SF-36 dimensions, PCS and MCS than for EQ-5D
Chakravorty 2002, UK[31]	SAHS with AHI≥15/hour	50 years (NR)	RCT	CPAP Lifestyle advice	32 21	16/ 8 14/ 11	0.73/ 0.77 * 0.77/ 0.77	• EQ-5D-3L UK value set • Standard gamble estimates were significantly lower than EQ-5D Index values: (0.32/ 0.55 for CPAP)
Mar 2003, Spain[32]	OSA ESS>10 & AHI>30/hour	53 years (100%)	Observational (before/ after)	CPAP	46	14/ NR	0.74/ 0.81 *	• EQ-5D-3L UK value set • Spanish sleep clinic, may not be generalisable to UK
McMillan 2014 & 2015, UK (PREDICT)[29 30]	OSA with ESS>9	70 years (82%)	RCT	CPAP BSC	140 138	12/10 12/ 8	0.666 QALYs 0.668 QALYs	• EQ-5D-3L UK value set • Results reported as Area under EQ-5D curve QALYs
Quinnell 2014, UK (TOMADO trial)[33]	ESS≥9 & AHI 5-30/hour	51 years (80%)	RCT (crossover)	No treatment MD1 MD2 MD3	21 20 18 15	10.1 8.5 8.0 7.7	0.85 0.86 0.86 0.87	• EQ-5D-3L UK value set • Crossover trial comparing mandibular devices • Results controlled for baseline

Source: CS Appendix H, Table 26, adapted by ERG

BSC best supportive care; CPAP Continuous positive airway pressure; SAHS sleep apnoea hypopnoea syndrome; AHI Apnoea hypopnoea index; MD mandibular device

4.2.7.2.2 EQ-5D 'bolt on' studies

The NICE Guide to the methods of technology appraisals states that the EQ-5D is the preferred measure of health-related quality of life to calculate QALYs for cost-effectiveness analyses.[19] The Guide does recognise that in some circumstances the EQ-5D may not be appropriate, in which case:

> "… qualitative empirical evidence should be provided on the lack of content validity for the EQ-5D, demonstrating that key dimensions of health are missing. This should be supported by evidence that shows that EQ-5D performs poorly on tests of construct validity and responsiveness in a particular patient population." (NICE Guide to the methods of technology appraisal 2013, paragraph 5.3.10)[19]

The company provide this argument in section B.3.4 of their submission. This includes reference to a 'bolt on' study by Yang et al. (2014), which reported that adding a 'sleep' domain to the EQ-5D Index did not improve its ability to predict an overall subjective assessment of HRQOL (EQ-5D VAS scores).[34] However, we note that a more recent study by Finch et al (2019) did find that items related to energy/ sleep and relationships were significantly associated with better prediction of EQ-5D VAS scores.[35] They also found that questions related to energy appeared to be better at explaining variations in HRQOL than sleep. This finding may explain the greater sensitivity of the SF-6D in OSA studies reported above, as the SF-6D includes an energy dimension.[36]

The Finch et al. study therefore lends support to the Company's contention that the lack of a sleep or energy/vitality dimension in the EQ-5D limits its ability to detect changes in health-related quality of life for people with EDS. We note, however, that the Finch et al. study uses the VAS as the outcome variable, and the VAS is not a choice-based measure and so is not a measure of 'utility' suitable for QALY calculations.

4.2.7.2.3 McDaid et al. 2007 mapping from ESS to utility

Mapping is another approach that may be used when EQ-5D utilities are not available or not appropriate. This method was used by the ERG for the 2008 NICE appraisal of CPAP for OSA (TA139).[15 16] McDaid et al. used a regression approach to estimate change in utility associated with change in ESS. This analysis was based on individual patient data from three cohorts: two with SF-6D utility estimates (n=294),[37 38] with values based on UK public preferences; and one with EQ-5D-3L 'UK Tariff' values (n=94).[39] McDaid et al. used a simple linear regression, as the model fit was not improved with 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 30. The SF-6D and EQ-5D models produced very similar estimates of the fall in utility associated with a one-point increase in ESS: 0.0095 for the SF-6D and 0.0097 for the EQ-5D.

4.2.7.3 NHWS mapping

The company use a similar approach to McDaid et al. to estimate the relationship between ESS and EQ-5D to inform the utility values in their model. This is based on individual-level data from the National Health and Wellness Survey (NHWS) 2016 (CS B.3.4.2.2 and Appendix M). Participants were recruited from online panels in five EU countries, including the UK, and included people who self-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 and followed the process for fitting mapping equations recommended by the NICE Decision Support Unit (DSU).[40] This included a number of steps:

- [redacted]
- [redacted]
- [redacted]

The final mapping is reported in CS section B.3.4.2.2 and illustrated in CS Figure 19, alongside the McDaid formula. The NHWS formula 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 formula. 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). 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 indicators for OSA with/without narcolepsy set to 0/1. This means that the model estimates utility for an OSA only cohort 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 OSA population. However, this does not matter because in the absence of a survival difference between the treatments, cost-effectiveness is driven by between-treatment differences in utility, not by absolute utility values.

The age coefficient in the NHWS formula is positive, so mean utility increases with age. We suggest that this lacks face validity over the modelled time horizon (from a starting age of 54 to a maximum age of 100). Given the company's other modelling assumptions, this positive age gradient does not affect the estimated QALY difference between solriamfetol and standard care.

The company notes the apparent contradiction between their use of an ESS to EQ-5D mapping and their contention that the EQ-5D could not capture improvements in quality of life related to ESS reductions in the TONES 3 study. They argue that this was related to the baseline characteristics of the TONES 3 population, who had high baseline EQ-5D Index scores, and hence little capacity for improvement. The mean EQ-5D Index score in the NHWS OSA without narcolepsy sample was [redacted]. This compares with [redacted] in TONES 3.

4.2.7.4 Time trade off estimates of patient/partner utilities

The company also conducted a time trade off study to estimate utility associated with descriptions of health states for people with OSA with EDS and their partners (CS B.3.4.4.2 and Appendix N). The process of developing the health state descriptions, recruitment of the general public sample, the time trade-off interview and data analysis and validation are well described and follow recommendations in NICE Decision Support Unit guidance.[41]

Eight health state descriptions were developed: four for patients on CPAP for OSA with different levels of EDS (none ESS≤10, mild ESS 11-14, moderate ESS 15-18 or severe ESS ≥19); and four for partners of people with these health states. The health states were valued by a sample of [redacted] people, selected to reflect the UK population (by age, gender and

location). Values were elicited in a face-to-face interview with a time-trade off (TTO) technique. Participants were also asked to complete a VAS valuation of each health state.

Mean TTO utilities for the patient and partner health states are shown in CS Table 32 and Figure 20. The patient TTO values are compared with the McDaid and NHWS ESS to EQ-5D mappings in Figure 21. This shows that the TTO estimates have a much steeper gradient across ESS values than either of the EQ-5D based mappings. The company suggests that this may be explained by either insensitivity of the generic EQ-5D measure to sleep or oversensitivity of the TTO valuations due to the emphasis on the impact of EDS in the health state descriptions.

As might be expected, TTO estimates for partner utilities are higher than patient utilities for the same patient health state. The company derive a simple linear formula estimating the partner utility as a function of patient utility (CS B.3.4.4.3 and Figure 23). Although the trend is reported as statistically significant, Figure 23 shows wide variations.

4.2.7.5 Utility values used in the model

The company uses the NHWS mapping in their base case and the McDaid formula and patient TTO estimates in scenarios. They also report scenarios for each set of patient utility estimates (NHWS, McDaid and TTO) plus partner utilities estimated using the relationship between partner and patient utilities derived from the TTO data. The base case values at treatment initiation are reported in CS Table 31.

TONES 3 did not detect a significant effect on EQ-5D utility scores: possibly because the EQ-5D is insensitive to the effect of daytime sleepiness, a lack of power in the trial, the study period being too short for changes to ingrained behaviour or expectations to occur or because the magnitude of treatment effect on the 0-1 utility scale required for QALY calculation was insufficient. It is also possible that benefits of ESS reduction may have been to some extent offset by adverse effects.

There is a paucity of other utility data from the literature with the same definitions of ‘responder’ and ‘non-responder’ as in the model. Published EQ-5D utilities for OSA are similar to, or a little lower than general population norms; and similar, or a little higher, for treated compared with untreated cohorts. In this situation, it is reasonable to consider a mapping approach, although this does introduce additional uncertainty. The McDaid formula found a consistent estimate of the relationship between utility and ESS across EQ-5D and SF-6D datasets.

The company's NHWS mapping from ESS to EQ-5D has some advantages. The dataset is large, and methods of analysis are well reported and appear thorough. However, 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 OSA in the UK.

Utilities estimated by applying the NHWS formula to ESS changes in TONES 3 are much lower than UK general population norms, EQ-5D scores from TONES 3 and 5 and reported utilities for OSA in the literature: so, may lack face validity. The increase in NHWS estimates of utility by age also lacks face validity over the modelled time horizon (from age 54 to 100 years).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.

The company's TTO estimates for patient utilities show a much sharper decline with increasing ESS than both of the mapping formulae. We consider that this is likely to be due to the high emphasis placed on daytime sleepiness in the TTO health state descriptions. This means that the results are unlikely to be comparable with utility values in other NICE appraisals based on the EQ-5D.

ERG conclusions on utilities

On balance, we agree with the company's use of the NHWS mapping formula in the base case, and the McDaid formula in a scenario. We note that the NHWS mapping coefficient for ESS scores between 12 and 24 is the most influential parameter, as reported in the company's deterministic decision analysis Tornado diagram (see Figure 11 below).

It is not clear if partner utilities should be included. The NICE Reference Case perspective on outcomes includes direct health effects for carers, and of course partners are not necessarily carers. However, paragraph 5.1.7 of the methods guide does refer to inclusion of "all direct health effects for patients or other people". We note the high uncertainty over the relationship between partner and patient utilities, as estimated from the TTO analysis.

4.2.8 Resources and costs

4.2.8.1 Drug acquisition

4.2.8.1.1 Standard care

All treatment arms considered in the company's analysis contained a standard care component to manage the underlying cause of OSA, thus the resource use and costs associated with standard OSA therapy are not modelled, and only the cost of solriamfetol as an add-on treatment is included.

4.2.8.1.2 Solriamfetol

The recommended starting dose of solriamfetol for patients with OSA is 37.5 mg once daily. Depending on clinical response, the dose may 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 (see SmPC[42]).

Solriamfetol is available as 75 mg and 150 mg tablets; administration of the 37.5 mg dose can be achieved by halving a 75 mg tablet.[42] The cost of treatment with 37.5 mg, 75 mg and 150 mg doses is £1,154, £2,308 and £3,232 per patient per year, respectively (CS Table 2).

The company state in the CS that "US data suggests a [redacted] dose split for the 37.5 mg, 75 mg and 150 mg doses, respectively" (CS page 169). In the company's base case, a lower proportion of patients on 150 mg dose is assumed (20%) in anticipation that "UK prescribers will be more conservative compared with those in the US" (CS section B.3.8.4.5), and the modelled split across all doses is 40/40/20.

In the open label phase of TONES 5, where investigators were protocol-driven to titrate from a starting dose of 75 mg to the highest tolerated dose, the split between 75 mg and 150 mg doses in the mITT population with OSA was [redacted] (CSR TONES 5 Table 14.2.1.2a).

ERG conclusion on drug acquisition costs

We could not verify the reported US dose use data (i.e. a [redacted] dose split for the 37.5 mg, 75 mg and 150 mg doses), but we adopt this assumption in our base case because UK evidence is not available. The 40/40/20 and 20/40/40 dose splits are explored in our scenario analyses.

4.2.8.2 Drug administration

Solriamfetol is orally administered and, therefore, incurs no administration costs.

4.2.8.3 Resource use

Health state unit costs and resource use are discussed in CS sections B.3.5.1.2 and B.3.5.2. We note that the TONES 5 CSR contains information on the number of physician visits, collected via a questionnaire and the mean healthcare costs, including the cost of hospitalisation due to serious AEs, incurred by patients on different doses of solriamfetol (see Table 40 and CSR TONES 5 Tables). TONES 5, however, did not have patients from the UK. Hence, the estimated resource use might not apply to the NHS.

4.2.8.3.1 Costs of doctor appointments

In the company's analysis, it is assumed that all patients continuing the solriamfetol 37.5 mg or 75 mg dose beyond 12 weeks would require one consultation to discuss a dose increase, whilst those who titrate to the 150 mg dose would require two consultations, each consultant contact would be 15 minutes with a hospital-based medical consultant at the cost of £27.25 per face-to-face contact based on Curtis and Burns 2019.[43]

4.2.8.3.2 Costs of managing adverse events

The company states that "all AEs in TONES 3 were transient and the majority were mild/moderate in severity, therefore in the base-case analysis, treatment-related AEs that did not lead to discontinuation were not considered." For those AEs that lead to treatment discontinuation, a general practitioner (GP) contact (at £37 per contact)[43] is included in the base case.

As mentioned above, in the TONES 5 trial there were instances of SAEs requiring inpatient hospitalisation or prolonging existing hospitalisation (as shown in Appendix Table 40). The estimated hospitalisation rates based on evidence reported in the TONES 5 CSR are shown in Table 28. The HRG codes which we believe are most relevant to hospital admissions in OSA patients with EDS, related to serious AEs are shown in Table 29 below.

Table 28 Estimated probability of hospitalisation per model cycle

Treatment	Hospitalisation (per year)
Solriamfetol 37.5 mg	0%[1]
Solriamfetol 75 mg	[redacted]
Solriamfetol 150 mg	[redacted][2]

[1] There were no patients with the modal dose of 37.5 mg in TONES 5.

[2] See Appendix Table 40. Note that some of the records in Table 40 were for the same patients and their inpatient admissions were recorded on the same day. If more than one record was made for the same patient on the same date, only one instance of hospitalisation was modelled to avoid double-counting.

Table 29 HRG codes for hospital admissions

Currency code	Currency description	National average unit cost [a]
DZ18D	Sleep Disorders Affecting Breathing, with Interventions, with CC Score 4+	£5,153
DZ18E	Sleep Disorders Affecting Breathing, with Interventions, with CC Score 0-3	£2,136

[a] National Schedule of Reference Costs - Year 2018-19 - All NHS trusts and NHS foundation trusts - non-elective long stay[44]

ERG conclusion on resource used and costs

TONES 5 CSR states that "approximately [redacted] of the subjects in the safety population changed doses twice during the study, and approximately [redacted] changed doses more than 4 times after the initial dose of 75 mg." Since the company include the costs of only one and two consultations in the solriamfetol 75 mg and 150 mg arms, respectively, the cost of doctor appointments for consultations on solriamfetol dose titration may have been underestimated. Including the cost of one additional consultation in the solriamfetol 75 mg and 150 mg arms increases the company's base-case ICER only marginally (by £40). Therefore, in the ERG analyses, we include the same costs of doctor appointments as in the company's base case.

Adding the cost of hospitalisation increases the company's base-case ICER with ERG corrections by approximately £1,000; when the disutility of hospitalisation (-0.01) is also applied, the ICER increases further, but only slightly.

In our base case, we model hospitalisation due to serious AEs (Table 40), stratified by treatment dose using the average cost for the relevant HRG codes (see Table 29). NB: Based on clinical input, AE-related hospitalisation in patients treated for EDS due to OSA is relatively rare in UK practice.

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 a deterministic base case analysis (CS Table 35) and a base case result that incorporates bootstrap sampling of IPD data (CS Table 36). In both tables, standard care without solriamfetol is compared to weighted costs and QALYs for three doses of solriamfetol with standard care. The company's base case results are presented below.

Table 30 Company base-case results – weighted ICER

Technologies	Total costs (£)	Total QALYs	Total LYG	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
Standard care without solriamfetol	£0	11.054	29.280			
Standard care with solriamfetol (40/40/20 37.5, 75, 150 mg)	£7,402	11.271	29.280	£7,402	0.217	£34,106

Source: CS Table 35
Abbreviations: ICER, incremental cost effectiveness ratio; LYG, life years gained; QALYs, quality adjusted life years.

Both base case analyses show similar results. We note that the company's base case result that incorporates bootstrapping (CS Table 36) is derived from a partial probabilistic analysis and is not informative since results based on a full probabilistic analysis are also presented (see Table 33 below).

5.2 Company's sensitivity analyses

The CS presents deterministic analyses, threshold analyses and scenario analyses. A probabilistic sensitivity analysis is also presented. We discuss these analyses below.

5.2.1 Deterministic sensitivity analyses

The company identified 10 parameters with the most significant impact on the ICER and presents results obtained by varying these parameters individually across a plausible range using either the 95% CI, or within +/- 20% of their base-case values where no estimates of precision were available. We deem this approach reasonable. A tornado plot and results table for this univariate analysis is presented below (see Figure 11 and Table 31). The results are most sensitive to assumptions around the quality-of-life NHWS mapping and market share for the three doses of solriamfetol. The results are also sensitive to

assumptions around discount rates for costs and outcomes and discontinuation due to loss of efficacy.

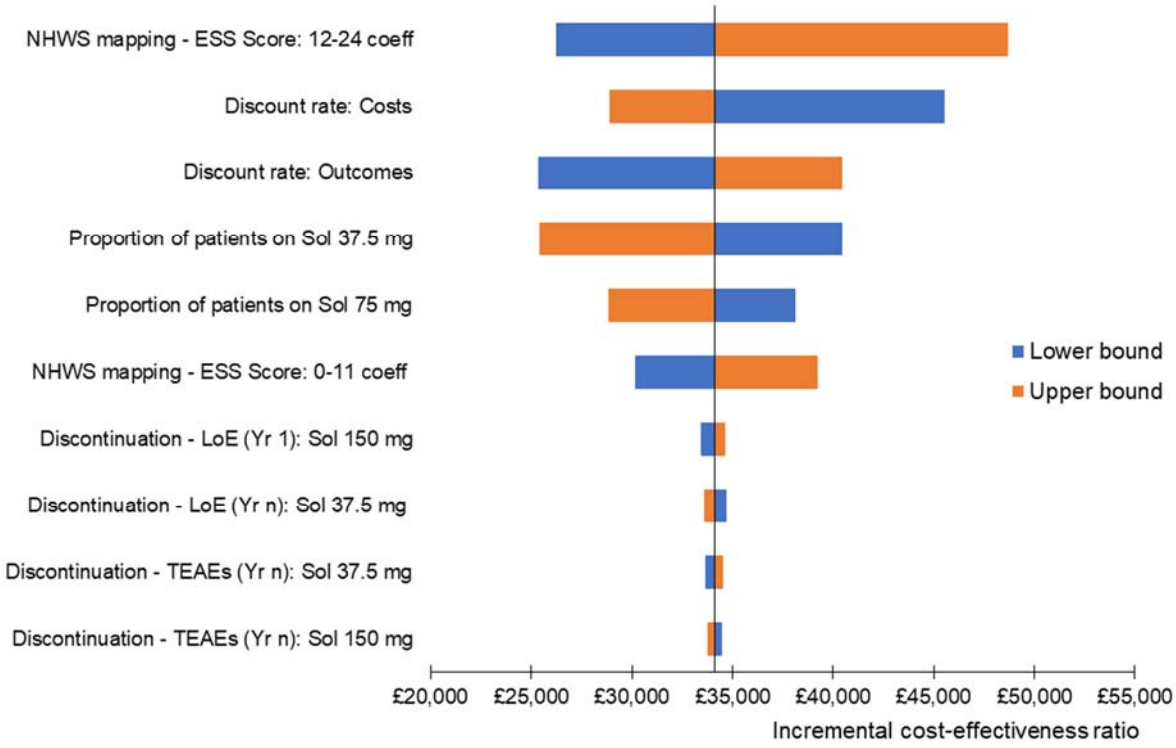


Figure 11 Company results of univariate analysis

Source: CS Figure 25
Abbreviations: ESS, Epworth Sleepiness Scale; ICER, incremental cost effectiveness ratio; LoE, loss of efficacy; TEAE, treatment emergent adverse events; Yr 1, Year one; Yr n, Years 2 and beyond

Table 31 Company results of univariate analysis

Variable (lower bound to upper bound; base case value)	ICER with lower bound	ICER with upper bound
NHWS mapping - ESS Score: 12-24 coefficient ([redacted] to [redacted]; base case [redacted])	£26,239	£48,707
Discount rate: Costs (0.0% to 6.0%; base case 3.5%)	£45,558	£28,881
Discount rate: Outcomes (0.0% to 6.0%; base case 3.5%)	£25,361	£40,472
Proportion of patients on Sol 37.5 mg (20.0% to 60.0%; base case 40.0%)	£40,482	£25,417
Proportion of patients on Sol 75 mg (20.0% to 60.0%; base case 40.0%)	£38,106	£28,836
NHWS mapping - ESS Score: 0-11 coefficient ([redacted] to [redacted]; base case [redacted])	£30,167	£39,227
Discontinuation - LoE (Yr 1): Sol 150 mg (1.8% to 5.4%; base case 3.6%)	£33,453	£34,654
Discontinuation - LoE (Yr n): Sol 37.5 mg (1.8% to 5.4%; base case 3.6%)	£34,726	£33,575

Variable (lower bound to upper bound; base case value)	ICER with lower bound	ICER with upper bound
Discontinuation - TEAEs (Yr n): Sol 37.5 mg (2.6% to 4.9%; base case 3.7%)	£33,638	£34,528
Discontinuation - TEAEs (Yr n): Sol 150 mg (2.6% to 4.9%; base case 3.7%)	£34,497	£33,752

Source: CS Table 38

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

5.2.2 Threshold analysis

In threshold analysis, the company sought to estimate the values at which standard care plus solriamfetol would become cost-effective for the 10 parameters identified in the deterministic sensitivity analysis as being the biggest drivers of cost effectiveness. Willingness-to-pay thresholds of £20,000 or £30,000 per QALY were explored, and results are presented below.

Table 32 Company threshold analysis

Variable	Base case	Value to achieve ICER of:	
	(Lower bound – Upper bound)	£20,000 per QALY	£30,000 per QALY
NHWS mapping - ESS Score: 12-24 coeff	[redacted] ([redacted] to -[redacted])	-0.02343*	-0.01510
Discount rate: Costs	3.5% (0.0% to 6.0%)	13.5%*	5.4%
Discount rate: Outcomes	3.5% (0.0% to 6.0%)	-2.3%*	1.9%
Proportion of patients on Sol 37.5 mg	40.0% (20.0% to 60.0%)	69.6%†	50.3%
Proportion of patients on Sol 75 mg	40.0% (20.0% to 60.0%)	83.5%†	56.1%
NHWS mapping - ESS Score: 0-11 coeff	[redacted] ([redacted] to [redacted])	-0.01989*	-0.00598*
Discontinuation - LoE (Yr 1): Sol 150 mg	3.6% (1.8% to 5.4%)	-17.9%*	-4.6%*
Discontinuation - LoE (Yr n): Sol 37.5 mg	3.6% (1.8% to 5.4%)	NA	39.1%*
Discontinuation - TEAEs (Yr n): Sol 37.5mg	3.7% (2.6% to 4.9%)	-17.0%*	-3.9%*
Discontinuation - TEAEs (Yr n): Sol 150 mg	3.7% (2.6% to 4.9%)	NA	39.7%*

Source: CS Table 39

Abbreviations: coeff, coefficient; ESS, Epworth Sleepiness Scale; ICER, incremental cost effectiveness ratio; LoE, loss of efficacy; NHWS, National Health and Wellness Survey; QALY, quality adjusted life year; TEAE, treatment emergent adverse events; Yr 1, Year one; Yr n, Years 2 and beyond.

* Outside credible range.

† Because the other doses are varied independently these scenarios are implausible (as the total share will exceed 100%).

5.2.3 Scenario analysis

The company explored a wide range of scenarios; however, in this section we discuss only the scenarios with the biggest influence on ICER. A scenario varying the model time horizon from five years to 35 years did not affect cost-effectiveness (CS Table 40). The ERG will explore a time horizon of one year.

A scenario to explore different definitions of response was explored by the company. We deem this scenario to be relevant to decision making as evidence from the literature suggests that a reduction in ESS scores of between 2–4 could be clinically relevant.[8 46] Assuming that response is a reduction in ESS ≥2 shifts the ICER upwards to £34,873 per QALY gained, while assuming that response is a reduction in ESS ≥4 shifts the ICER downwards to £32,482 per QALY gained (CS Table 42).

The company's scenario of 'true placebo' response for standard care without solriamfetol uses unadjusted IPD from TONES 3 for the different doses of solriamfetol while maintaining the baseline levels of EDS throughout the model time horizon for patients who did not receive the active treatment. In the ERG's preferred base case analysis, the company's assumption of centring was reversed, i.e. we use the actual changes in ESS from baseline after 12 weeks reported in the TONES 3 IPD data for all arms, including patients who did not receive the active treatment. The rationale and details of this assumption are discussed in section 6 below.

Other scenarios explored by the company are as follows: quality of life estimates based on TTO analysis; inclusion partner's health state utility decrements; variable ESS at entry by dose; baseline ESS at entry; and a subgroup analysis based on compliance to OSA therapy. We explore some of these analyses in detail and discuss further in our preferred analysis section 6.2.

5.2.4 Probabilistic sensitivity analysis

In the company's model, probability distributions were assigned to input parameters including costs, doses, probabilities and proportions. A full list of parameters varied by the company can be found in CS Table 33. We consider the choice of input distributions to be reasonable and we maintain these distributions in our analysis. In addition, the company accounted for uncertainty over parameters estimated from IPD data (the proportion of responders and mean ESS for responders and non-responders) by non-parametric bootstrap sampling. Bootstrap samples matching the sample size for each treatment are

drawn in each iteration of probabilistic sampling for a total of 5,000 Monte Carlo simulations. The company's results of the PSA are presented below. The PSA results are similar to the base-case results.

Table 33 Company probabilistic sensitivity analysis results

Treatment	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
Standard care	£0 (£0 - £0)	11.249 (11.239 - 11.259)			
Standard care with solriamfetol	£6,770 (£6,734 - £6,807)	11.428 (11.418 - 11.438)	£6,770	0.211	£32,092

Source: CS Table 37

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

5.3 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 (CS B.3.10.1). No further details are provided.

The ERG conducted a series of checks of the submitted model. This included checking that input parameters in the model matched the values cited in the CS and validating the results of analyses reported by the company. We also conducted 'white box' and 'black box' checks to validate the model: see our checklist in Appendix 9.4. We spotted a few errors, some of which were corrected by the company in their response to clarification questions (B5, B6, B9, C1 and C2). These have been incorporated in the description and results reported above. We subsequently identified some additional errors, which we have corrected below.

5.3.1 ERG corrections to the company's model

In the company's model, discontinuation rates due to TEAEs after the first year are estimated for standard care. We believe that the appropriate discontinuation rates for the standard care arm are those due to lack of efficacy and we apply this correction to the company's base case. The change in the company's base case results due to this correction is negligible. In addition, we are of the opinion that the Markov trace formulas in the company's model make assumptions that contradict the mutual exclusivity of events during transition from one state to another. We have edited the company's model to correct for this. We note however that it has a negligible effect on the ICERs.

6 EVIDENCE REVIEW GROUP'S ADDITIONAL ANALYSES

6.1 Exploratory analyses undertaken by the ERG

Below we summarise key issues affecting cost effectiveness and propose alternative assumptions and input parameters that inform the ERG's analyses (Table 34). A full list of issues that we considered in our critique of the company's cost-effectiveness model is provided in Appendix 9.5

In order to implement the non-centred version of the model, we had to make some structural changes. This included adding a fourth health state, Response No Treatment (RNT), to the company's three-state Markov model (as described in 4.2.2. above). This allowed us to model the persistence of improved ESS for a proportion of patients after discontinuation of solriamfetol because of TEAEs; in line with the inclusion of ESS response as a possibility for some patients in the standard care arm. The structure of the ERG 4-state non-centred version of the model is illustrated in Figure 12 below.

We compare results from the company's base case model with the ERG's 4-state, non-centred model (all other assumptions and parameters as in the company's base case) in Figure 13 and Figure 14 respectively. These figures include ESS, utility and the Markov trace graphs over the modelled time horizon.

The ERG's correction to the company's base case and a range of ERG scenario analyses are reported below in Table 35.

Table 34 Summary of key issues in the company's analysis and ERG's alternative analyses

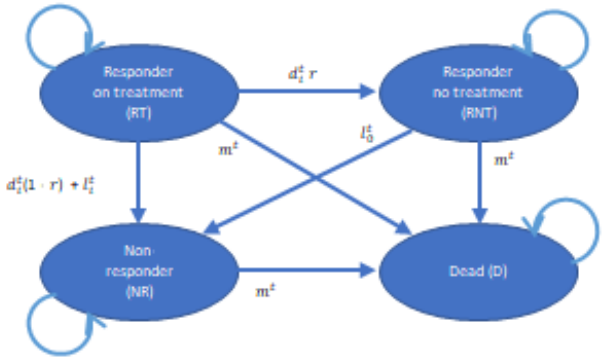
Issue	Company's analysis	ERG comments	ERG analysis
Decision problem			
Population characteristics	Base case: mITT population of TONES 3, excluding patients with ESS=10: [redacted] Scenarios: ESS>12 at baseline	For model parameterisation, the company use the baseline demographic and disease characteristics of the mITT population of the pivotal TONES 3 trial, excluding patients with ESS=10 at baseline, whereas in the European marketing authorisation for SOL, EDS is associated with the ESS score of at least 10 points. In the ERG base case, we use baseline characteristics of the whole mITT population from TONES 3, i.e. patients with baseline ESS score of at least 10 points. We conduct SAs for the threshold of ESS>10 and ESS>12.	Base case: the whole mITT population of TONES 3, including patients with ESS=10 at baseline Scenarios: - the patient sub-population with ESS>10 at baseline - the patient sub-population with ESS>12 at baseline
CPAP adherence	Base case: patients from the mITT population (TONES 3) with ESS>10 at baseline, regardless of their compliance to the primary OSA therapy Scenarios: for compliant and non-compliant patients at randomisation to TONES 3	The company's base case makes no distinction between compliant and non-compliant use of a primary OSA therapy. A subgroup analysis for patients who are compliant and non-compliant to the standard treatment has been conducted. Expert opinion suggests that in clinical practice compliance to CPAP is about 50%. We explore the effect of this assumption in a SA: we estimate an ICER assuming equal proportions of patients adherent and non-adherent with standard OSA therapy.	Base case: no change Scenarios: - no change - ICER for 50%/50% split for adherent/non-adherent patients
Clinical effectiveness			
Change in ESS: Centring	Base case: Changes in ESS modelled using IPD from TONES 3 'centred' to account for placebo effect Scenario: 'true placebo' response for standard care	We believe that there is insufficient evidence to justify the adjustment of the standard care arm and prefer to use trial data as observed (not centred) in our base case, and centred ESS in scenario analysis. Owing to a lack of long-term evidence, we assume that all patients continue standard OSA therapy regardless of their EDS status; the same assumption is made in the company's model.	Base case: raw/uncentred IPD from TONES 3 Scenario: centred IPD from TONES 3 (as in the company's base case)
Definition of	Base case: reduction in ESS≥3	There is a considerable variation in the definition of treatment	Base case: reduction ESS≥2

Issue	Company's analysis	ERG comments	ERG analysis
treatment response	Scenarios: reduction in ESS≥2 and ESS≥4	response in clinical practice, from the reduction in ESS of 2-3 points to normalisation in the ESS score, i.e. reduction in ESS below the ESS threshold defining EDS. We test this assumption in SAs.	Scenarios: - Reduction in ESS≥3 - Reduction in ESS≥4
Duration of treatment response	Base case: - responders: reduced ESS is maintained while on treatment, with ESS returning to mean baseline upon SOL discontinuation. - non-responders: ESS returns to mean baseline at the time of response assessment. Scenario: no change in ESS from baseline in non-responders.	In the company's base case, it is assumed that treatment response is maintained in responders for the duration of treatment, while for non-responders ESS returns to the mean baseline ESS at the time of response assessment. Over time, SOL treatment may be discontinued due to a lack of efficacy or incidence of TEAEs. In the ERG base case without centring, we assume that a 'response' is possible in a proportion of patients treated with standard care. We also assume that a proportion of patients who discontinue SOL due to a TEAE may retain their response. This is modelled using a fourth health state (response no treatment).	Base case: Non-centred 4-state model allows retention of response for a proportion of people who discontinue SOL due to AEs Scenario: no change
Loss of efficacy, adverse events and discontinuation			
Loss of efficacy	Base case: 3.6% loss of response per year for SOL Scenarios: none	In the company's base case, a proportion of SOL responders discontinue treatment and lose response due to a loss of efficacy over time. This rate is estimated from TONES 5 and assumed to be the same across all SOL doses. In our base case, we use dose-specific loss of efficacy rates for SOL, estimated from TONES 5 (see Appendix 9.1). As we also have SC 'responders' in our model, we also need a loss of efficacy rate for SC. We estimate this as a weighted mean of the SOL arms (weighted by the dose split, see below).	Base case: dose-specific rates loss of efficacy for SOL and SC Scenarios: - The company's base-case assumption - Loss of response in the SC arm increased by 20%
Discontinuation due to TEAEs	Base case: - 0% in induction - 3.7% per year in maintenance	It is assumed that the rate of discontinuation due to AEs during the initiation phase (i.e. decision tree component) was implicitly captured in the IPD and, therefore, not modelled separately. The estimate for the maintenance phase (the same for all	Base case: dose-specific rates of discontinuation Scenarios: the company's base-case assumption

Issue	Company's analysis	ERG comments	ERG analysis
	Scenarios: none	doses) is based on TONES 5. We use dose-specific discontinuation rates based on TONES 5 (see Appendix 9.1), estimated for the SOL dose split assumed in the ERG base case (see below).	
Adverse event costs and disutility	Base case: not modelled Scenarios: none	The CS reports on hospitalisation in OSA participants from TONES 5 who experienced SAEs. We include the hospitalisation costs in our analyses (see below).	Base case: hospitalisation due to SAEs (see below) Scenarios: see below
Resource use and costs			
Dose split for solriamfetol	Base case: 40/40/20 split for 37.5 mg, 75 mg and 150 mg Scenarios: - Disaggregated results by dose - 33/33/33 and [redacted] splits	In the ERG base case, we assume the [redacted] split using the US data, as UK evidence is not available. 40/40/20 and 20/40/40 dose splits are modelled in SAs.[redacted]	Base case: [redacted] Scenarios: - 40/40/20 split (as in the company's base case) - 20/40/40 split
The cost of hospitalisation due to SAEs	Base case: not modelled Scenarios: none	We model the costs of hospitalisation using the rates of hospitalisation in patients on different doses of SOL, observed in TONES 5 (Table 28), and the average cost per day for the relevant HRG codes (Table 29). NB: This cost is assumed only in patients receiving SOL. We do not model utility reduction due to hospitalisation since its effect on QALYs is likely to be negligible.	Base case: hospitalisation rates (Table 28), mean cost - £3,645 Scenario: not modelled
Other model assumptions			
Time horizon	Base case: lifetime (up to age 100 years) Scenarios: 5, 10, 15, 50 years	The lifetime time horizon is assumed in the company's and ERG base-case analyses. Varying the time horizon within 5-50-year range has virtually no effect on the ICER. We conduct an additional SA assuming the time horizon of 1 year (the follow-up in TONES 5).	Base case: no change Scenario: 1, 5, 10 and 50 years

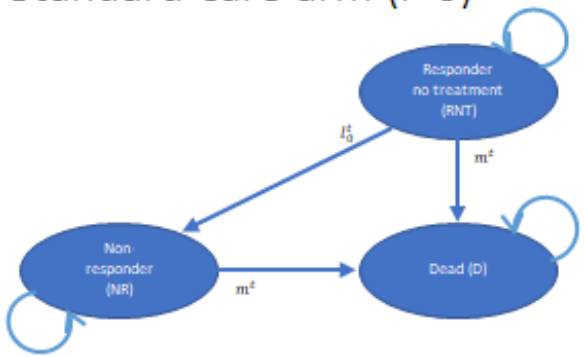
Abbreviations: ESS Epworth Sleepiness Scale, mITT modified intent-to-treat, SA scenario analysis, SAE, serious adverse event, SOL solriamfetol

Solriamfetol arms (i=1,2,3)



		TO			
		RT	*RNT*	*NR*	*D*
FROM	*RT*	$1 - d_i^t - l_i^t - m$	$d_i^t r$	$d_i^t(1-r) + l_i^t$	m
	RNT		$(1 - l_0^t - m)$	l_0^t	m
	NR			$(1-m)$	m
	D				1

Standard care arm (i=0)



		TO			
			RNT	*NR*	*D*
FROM	*RT*				
	RNT		$(1 - l_0^t - m)$	l_0^t	m
	NR			$(1-m)$	m
	D				1

r % responders at end of induction with standard care

d_i^t Probability of discontinuation due to adverse event during year t (t = 1, 2+) with treatment i (1=SOL 37.5, 2= SOL 75, 3 = SOL 150)

l_i^t Probability of loss of efficacy during year t (t = 1, 2+) with treatment i (0=SC, 1=SOL 37.5 mg ...)

m^t Mortality rate during year t (t = 1, 2, ..., T)

Figure 12 Structure of ERG 4-state non-centred Markov model

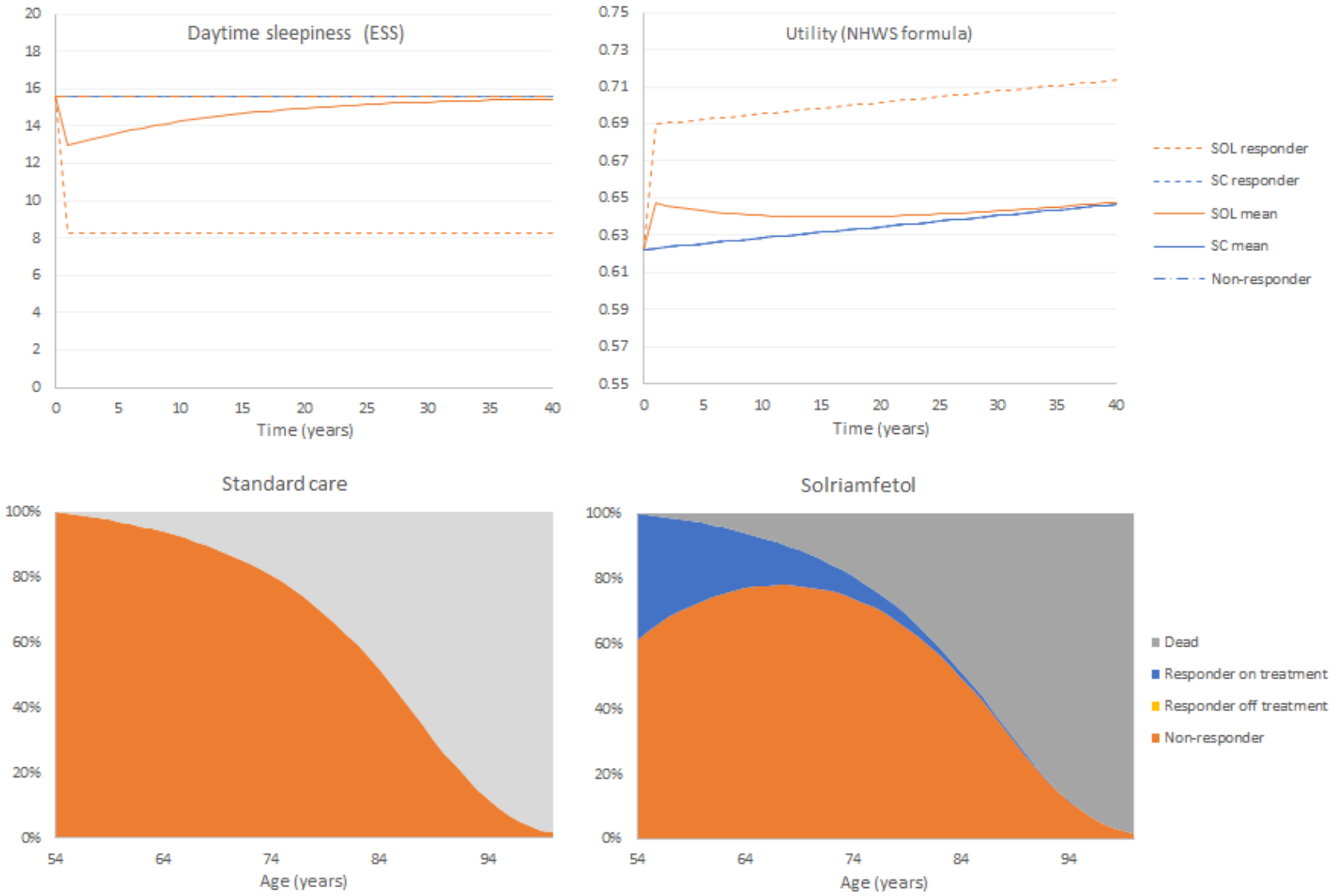


Figure 13 Summary of results from company 3-state model with centring (company base case assumptions)

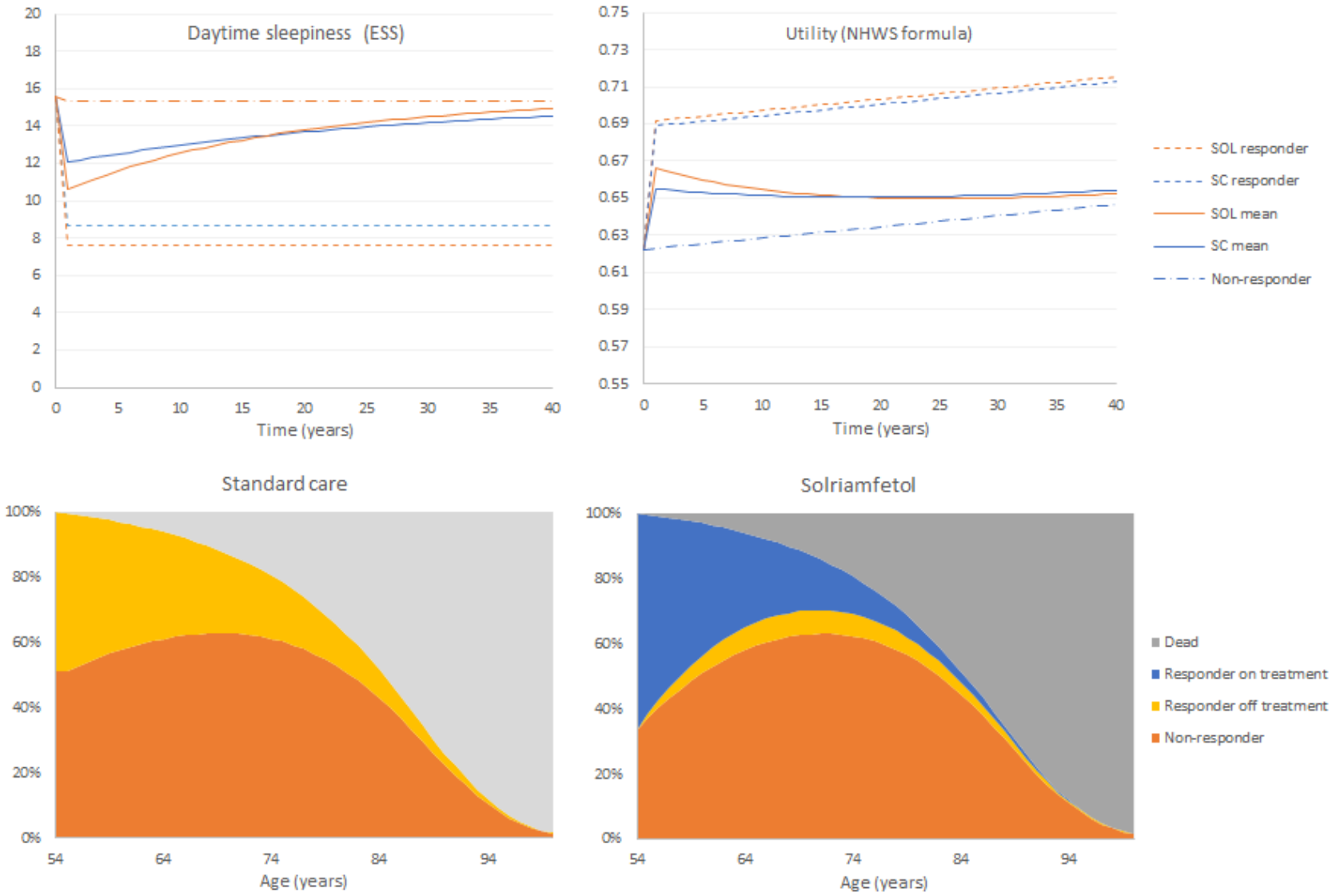


Figure 14 Summary of results from ERG 4-state model without centring (other company base case assumptions)

Table 35 Company base case (ERG corrected) and ERG scenario analyses

Individual scenarios on the base case	Treatment	Costs	QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
Company base case (with ERG corrections)	SC	£0	11.054	£0	0.000	£0
	SOL	£7,284	11.267	£7,284	0.213	£34,121
ESS≥10 at baseline (as in ERG base case)	SC	£0	11.129	£0	0.000	£0
	SOL	£6,970	11.322	£6,970	0.193	£36,118
ESS>12 at baseline	SC	£0	11.012	£0	0.000	£0
	SOL	£8,149	11.293	£8,149	0.281	£29,024
No centring + 4-state model	SC	£0	11.439	£0	0.000	£0
	SOL	£11,700	11.505	£11,700	0.066	£176,778
Timepoint of response assessment: 8 weeks	SC	£0	11.054	£0	0.000	£0
	SOL	£7,239	11.268	£7,239	0.214	£33,843
Time to treatment response: 2 weeks	SC	£0	11.054	£0	0.000	£0
	SOL	£7,284	11.267	£7,284	0.213	£34,121
Discontinuation rates: ERG base case for LoE and TEAEs	SC	£0	11.054	£0	0.000	£0
	SOL	£9,707	11.328	£9,707	0.274	£35,382
Treatment response: reduction in ESS≥2	SC	£0	11.054	£0	0.000	£0
	SOL	£8,195	11.289	£8,195	0.235	£34,887
Treatment response: reduction in ESS≥4	SC	£0	11.054	£0	0.000	£0
	SOL	£5,812	11.233	£5,812	0.179	£32,500
Cost of hospitalisation due to SAEs	SC	£0	11.054	£0	0.000	£0
	SOL	£7,489	11.267	£7,489	0.213	£35,079
[redacted]SOL dose split	SC	£0	11.054	£0	0.000	£0
	SOL	£8,316	11.277	£8,316	0.223	£37,219
20/40/40 SOL dose split	SC	£0	11.054	£0	0.000	£0
	SOL	£9,972	11.300	£9,972	0.246	£40,496
Model time horizon: 1 year	SC	£0	0.311	£0	0.000	£0
	SOL	£584	0.323	£584	0.012	£49,673
Model time horizon: 5 years	SC	£0	2.579	£0	0.000	£0
	SOL	£3,204	2.670	£3,204	0.091	£35,349
Model time horizon: 50 years	SC	£0	11.056	£0	0.000	£0
	SOL	£7,284	11.269	£7,284	0.213	£34,121
Compliant patients	SC	£0	11.151	£0	0.000	£0
	SOL	£6,940	11.342	£6,940	0.191	£36,329
Non-compliant patients	SC	£0	11.221	£0	0.000	£0
	SOL	£8,297	11.498	£8,297	0.277	£30,000
50%/50% split (compliant/ non-compliant)	SC	£0	11.186	£0	0.000	£0
	SOL	£7,619	11.420	£7,619	0.234	£32,586

SC: Standard Care; SOL: Solriamfetol combination

The ERG scenario that removed the company's assumption on centring and included the ERG's four-state model had the greatest effect on the results, with an ICER of £176,778 per QALY gained. Other key drivers of cost-effectiveness are the model time horizon (the ICER is higher with a shorter time horizon) and the solriamfetol dose split (the ICER is higher with more patients on the higher doses). Two subgroup analyses produced an ICER of £30,000 or below: restriction to patients with baseline ESS>12; and restriction to patients who were not compliant with standard OSA therapy at baseline.

6.2 ERG's preferred assumptions

Table 36 reports the cumulative change in the ICER resulting from the addition of each individual ERG assumption. The last two rows show the ERG's base case ICER, representing the combined effect of all these assumptions. Removing centring and assuming a four-state Markov model significantly increases the ICER. Our assumptions on treatment discontinuation reduce the ICER from this uncentred model.

The results of scenario analyses conducted on the ERG base case are presented in Table 37 below.

Table 36 ERG cumulative analysis and base case results

Cumulative analyses	Treatment	Costs	QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
Company base case (with ERG corrections)	SC	£0	11.054	£0	0.000	£0
	SOL	£7,284	11.267	£7,284	0.213	£34,121
ESS threshold ≥10	SC	£0	11.129	£0	0.000	£0
	SOL	£6,970	11.322	£6,970	0.193	£36,118
Treatment response:2	SC	£0	11.129	£0	0.000	£0
	SOL	£8,242	11.351	£8,242	0.222	£37,104
SOL dose split: [redacted]	SC	£0	11.129	£0	0.000	£0
	SOL	£9,470	11.364	£9,470	0.235	£40,310
Age-adjusted utility	SC	£0	10.417	£0	0.000	£0
	SOL	£9,470	10.652	£9,470	0.235	£40,310
Hospitalisation costs	SC	£0	10.417	£0	0.000	£0
	SOL	£9,745	10.652	£9,745	0.235	£41,480
Removing centring	SC	£0	10.870	£0	0.000	£0
	SOL	£14,772	10.813	£14,772	-0.057	Dominated
4-state model	SC	£0	10.870	£0	0.000	£0
	SOL	£14,772	10.917	£14,772	0.047	£315,667
Discontinuation rates	SC	£0	10.864	£0	0.000	£0
	SOL	£19,623	10.983	£19,623	0.119	£165,376
ERG base case	SC	£0	10.864	£0	0.000	£0
	SOL	£19,623	10.983	£19,623	0.119	£165,376

SC: Standard of Care; SOL: Solriamfetol combination.

Table 37 ERG scenario analyses

Individual scenarios on the base case	Treatment	Costs	QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
ERG base case	SC	£0	10.864	£0	0.000	£0
	SOL	£19,623	10.983	£19,623	0.119	£165,376
ESS>10 at baseline (company base case)	SC	£0	10.831	£0	0.000	£0
	SOL	£19,414	10.936	£19,414	0.104	£186,063
ESS>12 at baseline	SC	£0	10.746	£0	0.000	£0
	SOL	£19,892	10.883	£19,892	0.137	£146,596
Centring	SC	£0	10.417	£0	0.000	£0
	SOL	£13,112	10.722	£13,112	0.306	£42,877
Timepoint of response assessment: 8 weeks	SC	£0	10.865	£0	0.000	£0
	SOL	£19,604	10.983	£19,604	0.119	£165,231
Time to treatment response: 2 weeks	SC	£0	10.864	£0	0.000	£0
	SOL	£19,623	10.983	£19,623	0.119	£165,376
Discontinuation rates: company base case for LoE and TEAEs	SC	£0	10.870	£0	0.000	£0
	SOL	£14,772	10.917	£14,772	0.047	£315,667
Treatment response: reduction in ESS≥3	SC	£0	10.762	£0	0.000	£0
	SOL	£18,299	10.932	£18,299	0.170	£107,486
Treatment response: reduction in ESS≥4	SC	£0	10.724	£0	0.000	£0
	SOL	£16,558	10.886	£16,558	0.162	£102,051
Cost of hospitalisation due to SAEs	SC	£0	10.864	£0	0.000	£0
	SOL	£19,044	10.983	£19,044	0.119	£160,490
40/40/20 SOL dose split (company base case)	SC	£0	10.856	£0	0.000	£0
	SOL	£17,325	10.963	£17,325	0.107	£161,903
20/40/40 SOL dose split	SC	£0	10.891	£0	0.000	£0
	SOL	£23,643	11.048	£23,643	0.157	£150,753
Time horizon: 1 year	SC	£0	0.315	£0	0.000	£0
	SOL	£964	0.321	£964	0.005	£183,593
Time horizon: 5 years	SC	£0	2.597	£0	0.000	£0
	SOL	£6,591	2.634	£6,591	0.038	£175,466
Time horizon: 50 years	SC	£0	10.866	£0	0.000	£0
	SOL	£19,624	10.985	£19,624	0.119	£165,364
Compliant patients	SC	£0	10.911	£0	0.000	£0
	SOL	£19,201	11.017	£19,201	0.105	£182,476
Non-compliant patients	SC	£0	11.140	£0	0.000	£0
	SOL	£21,105	11.298	£21,105	0.158	£133,718
ICER for 50%/50% split (compliant/non-compliant)	SC	£0	11.026	£0	0.000	£0
	SOL	£20,153	11.157	£20,153	0.132	£153,222

SC: Standard Care; SOL: Solriamfetol combination.

Applying the company's assumption on discontinuation rates increases the ICER to £315,667 per QALY gained. Removing the ERG assumption on centring produces the most significant reduction in the ICER which drops to £42,877 per QALY gained. The assumptions of more stringent definitions of treatment response (ESS reductions of greater than or 3 or 4 points) also lead to reductions in the ICER.

The results of the ERG PSA analysis, based on 5000 simulations, are presented below in Table 38. The PSA ICER is lower than that of the deterministic base case, and this appears to reflect the high uncertainty associated with the ERG's assumptions on treatment discontinuation rates.

Table 38 ERG Probabilistic sensitivity analysis for the ERG base case

Treatment	Costs	QALYs	LYG	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
SC	£0	11,061	30.180	£0	0.000	£0
SOL	£25,489	11,284	30.180	£25,489	0.222	£114,459

7 END OF LIFE

The CS states that solriamfetol is not a life-extending treatment and does not meet NICE's end-of-life criteria. The ERG agrees with this statement.

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9 Appendices

9.1 Appendix: Discontinuation rates

The rates of discontinuation due to AEs in TONES 5 were 2.4% and 3.8% for 75 mg and 150 mg doses, respectively (CS section B.3.3.8); the observed rates of discontinuation due to loss of response were [redacted] and [redacted] (TONES 5 CSR Table 14.1.2.1a). The company state (CS page 146) that most AEs, 56.8%, occurred within the first 4 weeks of treatment.

We parameterise discontinuation rates in the first year assuming dose-specific rates observed in TONES 5 (see Table 39). The solriamfetol discontinuation rates in the consecutive years are assumed to equal 46.8% of those observed in the TONES 5 trial (based on 43.2% of AEs in 48 weeks). Due to lack of evidence on discontinuation rates for solriamfetol 37.5 mg in TONES 5, we assume that they are the same as those estimated for the 75 mg dose (see Table 39).

For the standard care arm, the modelled rates of loss of response to standard OSA therapy are based on the weighted average rates for the solriamfetol arms (Table 39), and the solriamfetol dose split assumed in our analysis (see section 4.2.8.1.2).

Note that these rates are applied in the ERG scenario for the company's 3-health-state model (see the model structure in Figure 3 and section 6). When the 4-health-state model structure is assumed (Figure 12), the discontinuation rates due to AEs are updated to take into account those patients who discontinue solriamfetol due to serious AEs but remain responders (see section 4.2.6.4 and section 6).

Table 39 Dose specific rates of discontinuation and loss of response

Drug		Discontinuation rate			
		Lack of efficacy		TEAEs	
		Year 1	Year n	Year 1	Year n
Solriamfetol	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

[1] The discontinuation rates for solriamfetol 37.5 mg dose are assumed to be same as for 75 mg.

9.2 Appendix: Hospitalisation in OSA patients from TONES 5

According to TONES 5 CSR (page 265), most TEAEs observed in the study population resolved in about a week while continuing treatment with solriamfetol, but there were instances of SAEs requiring inpatient hospitalisation or prolonging existing hospitalisation (see Table 40 below).

Table 40 Hospitalisation due to serious AEs

[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Source: based on CONFIDENTIAL. Jazz Pharmaceuticals TONES 5 CSR End of text safety tables.pdf

9.3 Appendix: Distribution of the change in ESS from baseline at week 12

Figure 15 Change in ESS from baseline at week 12: whole mITT population from TONES 3 (i.e. patients with baseline ESS of at least 10 points)

9.4 Appendix: ERG model checks

ERG checks on model	*Initials*	*Priority*	*OK?*	*Comments*
Face validity *Are the results logical and clinically plausible?*				
Check ESS and utility results over time, means and responder/non-responder values	JL	High	Yes	Added graphs of ESS and utility (mean, responder and non-responder) values to model. As expected for company centred model. Also checked for non-centred version, which led to investigation of discontinuation and loss of response rates.
The same discontinuation rate due to TEAEs (3.7%) was applied to standard care and all other doses of Sol post year 1.	OO	Medium	No	Error in model over loss of effect rate for SC (TEAE rate used). For Sol, we include dose-specific AE rates.
Utility increases with age across the model time horizon because of the positive age coefficient in the NHWS formula.	JL	Low	No	Does not affect incremental QALYs but remove age increment in ERG analysis.
White box *Manual checks of formulae and VBA*				
Company's implementation of bootstrapping	OO	High	No	Company VBA code for running bootstrap results is wrongly automated. ERG correction
Results of company's deterministic (univariate analysis).	OO	High	Yes	Corrected in updated company model with CR
Results for company's threshold analysis	OO	High	Yes	Corrected in updated company model with CR
Estimation of drug costs	OO	High	Yes	formulas are okay
Regression formulas for utility	OO	High	Yes	formulas are okay
Markov traces for all treatments	OO	High	Yes	formulas are okay
Replication *Recode sections of model to check calculations*				
Check IPD calculations, including centring, calculation of mean ESS for responders/ non-responders and utility calculations	JL	High	Yes	Developed 'ERG simple model'
Black box *Change input parameters and check results are plausible - from Tech-VAR*				
Does the technology acquisition cost increase with higher prices?	OO	Medium	Yes	
Does the sum of the patients in health states sum to the cohort size?	OO	Medium	Yes	
Check probabilities and proportion of cohort in each state are in [0,1]	OO	Medium	Yes	
Check if all probabilities are less than or equal to 1.	OO	Medium	Yes	
Check number of dead is greater or equal to previous periods	OO	Medium	Yes	
Set all utilities to 1, QALYs same as life years?	OO	Medium	Yes	
Set all utilities to 0, QALYs are zero?	OO	Medium	Yes	

Decrease utilities for health states, total QALYs decrease?	OO	Medium	Yes	
Put mortality rates to 0, patients never die?	OO	Medium	Yes	
Put mortality rates to extremely high, patients die in the first few cycles?	OO	Medium	Yes	
Are the utility estimates equal or lower than for the general population?	OO	Medium	Yes	
Set all costs to £0, total costs are zero?	OO	Medium	Yes	
Increase treatment acquisition costs, do total costs increase?	OO	Medium	Yes	
Are incremental life years and QALYs plausible, given clinical effectiveness?	OO	Medium	Yes	
Are incremental cost results plausible, given treatment costs?	OO	Medium	Yes	
Total life years greater than total QALYs?	OO	Medium	Yes	
Do life years and QALYs decrease with a shorter time horizon?	OO	Medium	Yes	
Is half cycle correction implemented correctly?	OO	Medium	Yes	
Undiscounted results greater than discounted results?	OO	Medium	Yes	
Set discount rate to 0, are discounted and undiscounted results the same?	OO	Medium	Yes	
Set discount rate to a higher values, do discounted results decrease?	OO	Medium	Yes	
Set discount rate to extremely high value, are results similar to those in the first cycles?	OO	Medium	Yes	
Are all necessary parameters included in the DSA?	OO	Medium	Yes	
Are ranges in DSA based on confidence intervals of the parameters?	OO	Medium	Yes	
Are results for upper and lower bounds of parameters plausible?	OO	Medium	Yes	
Have the appropriate distributions been used for the parameters in the PSA?	OO	Medium	Yes	
Are PSA results similar to deterministic results?	OO	Medium	Yes	
Do two runs of the PSA produce similar results?	OO	Medium	Yes	
Is the CEAC in line with scatterplots and efficiency frontier?	OO	Medium	Yes	
Is the sum of all CEAC lines equal to 1 for WTP values?	OO	Medium	Yes	
Are scenario analysis results plausible and in line with expectations?	OO	Medium	Yes	
Do explored analyses provide a balanced view on the structure uncertainty?	OO	Medium	Yes	
Are there any important omitted scenario analyses?	OO	Medium	Yes	See list of ERG scenarios

9.5 Appendix: ERG commentary on issues in the company's economic analysis

Issue	Company's analysis	ERG comments	ERG analysis
Decision problem			
Population characteristics	Base case: baseline demographic characteristics from the mITT population of TONES 3: - mean age: [redacted] years - female: [redacted]% Mean baseline ESS from the mITT population of TONES 3, excluding patients with ESS=10: [redacted] Scenarios: ESS>12 at baseline	For model parameterisation, the company use the baseline demographic and disease characteristics of the mITT population of the pivotal TONES 3 trial, excluding patients with ESS=10 at baseline (CS Table 25), whereas in the European marketing authorisation for SOL (CS Appendix C), EDS is associated with the ESS score of at least 10 points. The company do not provide a rationale for exclusion of patients with baseline ESS=10 from their analysis. As stated in CS KOL Clinical Practice Interviews, the decision to start treatment may depend on other factors, such as driving status, and treatment can be initiated in patients whose driving is affected even if their EDS is low. Therefore, excluding patients with ESS=10 from the analysis may not be justifiable. Clinical advice to the ERG suggests that the average ESS score at baseline observed in the TONES 3 trial is higher than that in patients with residual EDS in clinical practice. In the ERG base case, we use baseline characteristics of the whole mITT population from TONES 3, i.e. patients with baseline ESS score of at least 10 points. We conduct SAs for the threshold of ESS>10 and ESS>12.	Base case: baseline demographic and disease characteristics from the whole mITT population of TONES 3, including patients with ESS=10 at baseline: - mean age: [redacted] years - female: [redacted]% - mean baseline ESS: [redacted] Scenarios: - the patient sub-population with ESS>10 at baseline (as in the company's base case) - the patient sub-population with ESS>12 at baseline
CPAP adherence	Base case: patients from the mITT population (TONES 3) with ESS>10 at baseline, regardless of their compliance to the primary OSA therapy Scenarios: for compliant and non-compliant patients at randomisation to TONES 3	The company's base case makes no distinction between compliant and non-compliant use of a primary OSA therapy (as defined in CS section B.3.9.1 page 191). A subgroup analysis for patients who are compliant and non-compliant to the standard treatment has been conducted. NB: In TONES 3, 70% of patients were compliant to standard OSA treatment at randomisation to the trial. Expert opinion suggests that in clinical practice compliance to CPAP is about 50%. We explore the	Base case: no change Scenarios: - no change - ICER for 50%/50% split for adherent/non-adherent patients

Issue	Company's analysis	ERG comments	ERG analysis
		effect of this assumption in a SA: we estimate an ICER assuming equal proportions of patients adherent and non-adherent with standard OSA therapy.	
Mortality	Base case: sex- and age-specific all-cause mortality (based on the Office of National Statistics life tables[18]) Scenario: none	Solriamfetol is assumed to have no impact on mortality, and therefore, general population mortality is assumed. The ERG agrees with this approach. Changes in cardiovascular risk factors (e.g. systolic blood pressure) with the addition of solriamfetol to primary OSA therapy in TONES 3 were small, and there is no evidence that use of solriamfetol would change the incidence of road traffic accidents.	Base case: no change Scenarios: none
Comparators	Base case: the primary OSA therapy (as described in section 2.2.3) Scenarios: none	We have been advised that sleep specialists may sometimes prescribe modafinil off-license for EDS due to OSA. However, this would only be for a minority of patients, and non-specialists are unlikely to be prepared to prescribe modafinil.	Base case: no change Scenario: none
Clinical effectiveness			
Change in ESS: Centring	Base case: Changes in ESS modelled using IPD from TONES 3 'centred' (as described in section 4.2.6.1) to account for placebo effect Scenario: 'true placebo' response for standard care	We believe that there is insufficient evidence to justify the adjustment of the standard care arm and prefer to use trial data as observed (not centred) in our base case, and centred ESS in scenario analysis. Owing to a lack of long-term evidence, we assume that all patients continue standard OSA therapy regardless of their EDS status; the same assumption is made in the company's model.	Base case: raw/uncentred IPD from TONES 3 Scenario: centred IPD from TONES 3 (as in the company's base case)
Definition of treatment response	Base case: reduction in ESS≥3 Scenarios: reduction in ESS≥2 and ESS≥4	There is a considerable variation in the definition of treatment response in clinical practice, from the reduction in ESS of 2-3 points to normalisation in the ESS score, i.e. reduction in ESS below the ESS threshold defining EDS (CS KOL Clinical Practice Interviews and clinical advice to the ERG). We, therefore, test this assumption in scenarios.	Base case: reduction ESS≥2 Scenarios: - Reduction in ESS≥3 - Reduction in ESS≥4
Timing of response assessment	Base case: 12 weeks	In the model, the response status is assessed at 12 weeks of treatment (as in TONES 3). We have been advised that in	Base case: no change

Issue	Company's analysis	ERG comments	ERG analysis
	Scenario: none	clinical practice, patients are typically seen every 6-12 weeks. We conduct a SA using uncentred ESS at 8 weeks.	Scenario: 8 weeks
Time to treatment response	Base case: 1 week Scenarios: none	Improvement in ESS (and the associated impact on QoL) is assumed to occur one week after treatment initiation. We explore the effect of an increased time to response in scenario analysis.	Base case: no change Scenario: 2 weeks
Duration of treatment response	Base case: - responders: reduced ESS is maintained while on treatment, with ESS returning to mean baseline upon SOL discontinuation. - non-responders: ESS returns to mean baseline at the time of response assessment. Scenario: no change in ESS from baseline in non-responders.[1]	In the company's base case, it is assumed that treatment response is maintained in responders for the duration of treatment, while for non-responders ESS returns to the mean baseline ESS at the time of response assessment (12 weeks in the base case). Over time, solriamfetol treatment may be discontinued due to a lack of efficacy or incidence of TEAEs. In the ERG base case without centring, we assume that a 'response' is possible in a proportion of patients treated with standard care. We also assume that a proportion of patients who discontinue solriamfetol due to a TEAE may retain their response. This is modelled using a fourth health state (response no treatment).	Base case: Non-centred 4-state model allows retention of response for a proportion of people who discontinue solriamfetol due to Scenario: no change
Loss of efficacy, adverse events and discontinuation			
Loss of efficacy	Base case: 3.6% loss of response per year for SOL Scenarios: none	In the company's base case, a proportion of solriamfetol responders discontinue treatment and lose response due to a loss of efficacy over time. This rate is estimated from TONES 5 and assumed to be the same across all SOL doses. In our base case, we use dose-specific loss of efficacy rates for SOL, estimated from TONES 5 (see Appendix 9.1). As we also have SC 'responders' in our model, we also need a loss of efficacy rate for SC. We estimate this as a weighted mean of the SOL arms (weighted by the ERG dose split, as below).	Base case: dose-specific rates loss of efficacy for SOL & SC Scenarios: The company's base-case assumption Loss of response in the SC arm increased by 20%
Discontinuation due to TEAEs	Base case:	It is assumed that the rate of discontinuation due to AEs during the initiation phase (i.e. decision tree component) was implicitly	Base case: dose-specific rates of discontinuation

Issue	Company's analysis	ERG comments	ERG analysis
	- 0% in induction - 3.7% per year in maintenance Scenarios: none	captured in the IPD and, therefore, not modelled separately. The estimate for the maintenance phase (the same for all doses) is based on TONES 5. We use dose-specific discontinuation rates based on TONES 5 (see Appendix 9.1), estimated for the solriamfetol dose split assumed in the ERG base case (see below).	Scenarios: the company's base-case assumption
Adverse event costs and disutility	Base case: not modelled Scenarios: none	The CS reports on hospitalisation in OSA participants from TONES 5 who experienced SAEs. We include the hospitalisation costs in our analyses (see below).	Base case: hospitalisation due to SAEs (see below) Scenarios: see below
Health state utilities			
Patient utility for OSA with EDS	Base case: EQ-5D-5L utilities estimated as a function of ESS from de novo mapping with 2016-2017 EU5 NHWS data Scenarios: - EQ-5D-3L utilities mapped from ESS (McDaid 2007) - TTO utility for health state descriptions with different levels of ESS severity from survey of general public	EQ-5D-5L results from the TONES 3 trial are not used in the economic model. [redacted]. The company argue that this is because the EQ-5D is insensitive because of the high baseline values in the TONES 3 population. We acknowledge this point but note that the lack of evidence of effect from the EQ-5D-5L in TONES 3 does raise uncertainty over the effectiveness of SOL at improving utility in this population. The company base case model estimates utility as a function of ESS and other patient characteristics, based on a new mapping from NHWS data. NHWS coefficients are the most influential model parameters in the company base case. Two alternative sources of utility estimates are used in scenario analysis: the McDaid et al. mapping from the NICE appraisal of CPAP for OSA (TA139); and a new TTO study. The ERG agrees that the NHWS mapping is the best available source of utility estimates, and the McDaid formula is a suitable alternative. We do not favour use of the TTO estimates.	Base case: no change Scenarios: no change
Partner utilities	Base case: not included	A simple linear relationship was assumed between patient and	Base case: no change

Issue	Company's analysis	ERG comments	ERG analysis
	Scenarios: Utilities for partners of people with EDS due to OSA estimated as a function of patient utility (formula from TTO study)	partner utilities, and used in scenario analysis (applied to NHWS, McDaid and TTO patient utility estimates). For these scenarios, The second SA assumed that 66% of patients would be living as a couple and thus have partners who could be affected by their EDS; the partner would be of the same age, and die at the same rate as the patient, using the standard life tables.[18]	Scenarios: no change
Resource use and costs			
Solriamfetol acquisition cost	Base case: The acquisition cost includes: - The cost of SOL treatment in all patients during the initiation phase without up-titration - The subsequent cost of treatment in responders until SOL discontinuation - It is assumed that in non-responders SOL is discontinued immediately after the assessment of treatment response. Scenarios: none	The company does not model up-titration from the starting dose of 37.5 mg: it is assumed that patients are given the highest dose they are titrated to from the start of treatment. The base case assumes a 40/40/20 split for SOL 37.5 mg, 75 mg and 150 mg (see below). We conduct a SA for up-titration during the treatment initiation period.	Base case: no change Scenario: up-titration during the treatment initiation period
Dose split for solriamfetol	Base case: 40/40/20 split for 37.5 mg, 75 mg and 150 mg Scenarios: - Disaggregated results by dose - 33/33/33 and 25/50/25 splits	In the ERG base case, we assume the [redacted] split using the US data, as UK evidence is not available. 40/40/20 and 20/40/20 dose splits are modelled in SAs.[redacted]	Base case: [redacted] Scenarios: - 40/40/20 split (as in the company's base case) - 20/40/40 split
The cost of hospitalisation due	Base case: not modelled Scenarios: none	We model the costs of hospitalisation using the rates of hospitalisation in patients on different doses of solriamfetol,	Base case: hospitalisation rates (Table 28), mean cost -

Issue	Company's analysis	ERG comments	ERG analysis
to SAEs		observed in TONES 5 (Table 28), and the average cost per day for the relevant HRG codes (Table 29). NB: This cost is assumed only in patients receiving SOL. We do not model utility reduction due to hospitalisation since its effect on QALYs is likely to be negligible.	£3,645 Scenario: the assumption as in the company's base case (i.e. not modelled)
The cost of medical appointments	Base case: one incremental consultation with a hospital-based medical consultant for patients continuing SOL 37.5 or 75 mg doses beyond 12 weeks, and two consultations for those who titrate to SOL 150 mg, assuming 15 minutes per consultation at the cost of £27.25 per consultation Scenario: excluding the cost of medical appointments[1]	The company assume that the introduction of SOL would not require an additional consultation for treatment initiation, but one appointment to discuss titration to a higher dose would be required. Our experts agree with this assumption.	Base case: no change Scenario: no change
Other model assumptions			
Time horizon	Base case: lifetime (up to age 100 years) Scenarios: 5, 10, 15...50 years	The lifetime time horizon is assumed in the company's and ERG base-case analyses. Varying the time horizon within 5-50 year range has virtually no effect on the ICER. We conduct an additional SA assuming the time horizon of 1 year (the follow-up in TONES 5).	Base case: no change Scenario: 1 year
Discounting	Base case: 3.5% Scenarios: 0% and 6%	The discount of 3.5% per year is applied to costs and QALYs in the base case, and 0% and 6% SAs. According to the company's DSA, this is one of key model parameters.	Base case: no change Scenarios: no change

Abbreviations: DSA deterministic sensitivity analysis, ESS Epworth Sleepiness Scale, mITT modified intent-to-treat, OSA obstructive sleep apnoea, SA scenario analysis, SAE, serious adverse event, SOL solriamfetol

[1] This analysis is not reported in the CS but available in the company's economic model

CONFIDENTIAL

Single technology appraisal

Addendum to ERG critique of technical engagement response: list price cost-effectiveness results

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

[Contains confidential commercial information]

Produced by Southampton Health Technology Assessments Centre (SHTAC)

Addendum date 8 March 2021

Commercial in confidence information is underlined and highlighted in blue.

The analyses in this addendum were produced by the ERG using solriamfetol list prices:

- £177.52 per pack of 28 x 75 mg film-coated tablets
- £248.64 per pack of 28 x 150 mg film-coated tablets

Table 1 shows deterministic list price results for the company's revised model following technical engagement, with selected scenarios presented by the company. Probabilistic results for the company's base case are similar to the deterministic results (Table 2)

Table 1 Company's revised base case and scenarios: deterministic with list price

Scenario	Treatment	Costs	QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
Company's revised base case	SC	£0	11.524			
	SOL	£10,889	11.906	£10,889	0.383	£28,453
Compliant to a primary OSA therapy	SC	£0	11.382			
	SOL	£10,277	11.727	£10,277	0.345	£29,824
Non-compliant to a primary OSA therapy	SC	£0	11.767			
	SOL	£12,005	12.226	£12,005	0.459	£26,183
Treatment response: reduction in ESS≥2	SC	£0	11.524			
	SOL	£12,021	11.936	£12,021	0.412	£29,183
Treatment response: reduction in ESS≥4	SC	£0	11.524			
	SOL	£8,844	11.851	£8,844	0.327	£27,066
[redacted] SOL dose split (ERG base case)	SC	£0	11.524			
	SOL	£12,645	11.937	£12,645	0.413	£30,635
QoL estimates from McDaid mapping	SC	£0	13.963			
	SOL	£10,889	14.304	£10,889	0.341	£31,929
QoL estimates from TTO analysis	SC	£0	12.028			
	SOL	£10,889	12.864	£10,889	0.836	£13,025
Partner utilities (NHWS mapping)	SC	£0	20.605			
	SOL	£10,889	21.129	£10,889	0.524	£20,793
Partner utilities (McDaid mapping)	SC	£0	23.943			
	SOL	£10,889	24.410	£10,889	0.467	£23,333
Partner utilities (TTO)	SC	£0	21.296			
	SOL	£10,889	22.440	£10,889	1.144	£9,518

SC: standard care; SOL: solriamfetol combination
Source: Produced by ERG from the Company's model submitted after technical engagement

Table 2 Company's revised base case: probabilistic analysis with list price

Scenario	Treatment	Costs	QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
Company's revised base case	SC	£0	11.872			
	SOL	£9,856	12.237	£9,856	0.365	£27,010

SC: standard care; SOL: solriamfetol combination
Source: Produced by ERG from the Company's model submitted after technical engagement

Additional ERG scenarios applied to the company's revised base case are shown in Table 3. These analyses were conducted with an adapted version of the company's model developed by the ERG. This model was developed to explore the effect of removing the 'centring' adjustment for placebo effects and other uncertainties. It also includes some minor edits to the company's base case (NHWS coefficients from Kantar report dated 1/2/21 and discontinuation calculations), which explain the small differences the revised company base case results in Table 1 and Table 3.

Table 3 Company revised base case (ERG corrected) and ERG scenario analyses: deterministic with list price

Individual scenarios on the base case	Treatment	Costs	QALYs	Incremental costs (£)	Incremental QALYs	ICER £/QALY
Company base case (with ERG corrections)	SC	£0	10.033			
	SOL	£10,795	10.412	£10,795	0.379	£28,485
No centring + 4-state model	SC	£0	10.516			
	SOL	£15,985	10.716	£15,985	0.199	£80,151
Timepoint of response assessment: 8 weeks	SC	£0	10.033			
	SOL	£10,754	10.412	£10,754	0.379	£28,348
Treatment response: reduction in ESS≥2	SC	£0	10.033			
	SOL	£11,916	10.441	£11,916	0.408	£29,215
Treatment response: reduction in ESS≥4	SC	£0	10.033			
	SOL	£8,767	10.356	£8,767	0.324	£27,096
Cost of hospitalisation due to SAEs	SC	£0	10.033			
	SOL	£11,122	10.412	£11,122	0.379	£29,350
[redacted] SOL dose split	SC	£0	10.033			
	SOL	£12,539	10.442	£12,539	0.409	£30,665
20/40/40 SOL dose split	SC	£0	10.033			
	SOL	£15,318	10.494	£15,318	0.461	£33,235
Model time horizon: 1 year	SC	£0	0.275			
	SOL	£622	0.292	£622	0.017	£37,145
Model time horizon: 5 years	SC	£0	2.286			
	SOL	£3,664	2.415	£3,664	0.128	£28,566
Compliant patients	SC	£0	9.939			
	SOL	£10,185	10.280	£10,185	0.341	£29,859
Non-compliant patients	SC	£0	10.181			
	SOL	£11,908	10.636	£11,908	0.454	£26,210
ICER for 50%/50% split (compliant/ non-compliant)	SC	£0	10.060			
	SOL	£11,047	10.458	£11,047	0.398	£27,775

SC: standard care; SOL: solriamfetol combination
Source: Produced by ERG from an adapted version of the Company's model

Table 4 shows how ERG preferred assumptions change the ICER from the company's revised base case. The four changes are shown cumulatively: so, each row includes the changes in previous rows. ERG changes to the definition of treatment response, assumed dose split and hospitalisation costs cause small increases in the ICER. The ERG model adaptation to remove the company's 'centring' placebo adjustment had a large effect, increasing the ICER to over £100,000 per QALY gained.

Table 4 ERG cumulative analysis and base-case results for population with ESS > 12 at baseline: deterministic, produced by ERG using list price

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

SC: standard care; SOL: solriamfetol combination.
Source: Produced by ERG from an adapted version of the Company's model

Scenario analysis conducted on the ERG base case is shown in Table 5. The ICER was most sensitive to reverting to the company's placebo-adjustment (centring). Other scenarios that caused a sizable reduction in the ICER were: increases in the ESS response threshold; and increases in the loss of response rate for standard care.

Table 5 ERG scenario analyses: deterministic, produced by ERG using list price

Individual scenarios on the base case	Treatment	Costs	QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
ERG base case	SC	£0	10.638			
	SOL	£19,978	10.810	£19,978	0.171	£116,674
With centring and 3-state model	SC	£0	10.033			
	SOL	£14,324	10.474	£14,324	0.441	£32,465
Timepoint of response assessment: 8 weeks	SC	£0	10.639			
	SOL	£19,959	10.810	£19,959	0.171	£116,560
Treatment response: reduction in ESS≥3	SC	£0	10.525			
	SOL	£18,691	10.745	£18,691	0.220	£84,933
Treatment response: reduction in ESS≥4	SC	£0	10.469			
	SOL	£17,430	10.698	£17,430	0.229	£76,142
Without the cost of hospitalisation due to SAEs	SC	£0	10.638			
	SOL	£19,389	10.810	£19,389	0.171	£113,232
40/40/20 SOL dose split (company base case)	SC	£0	10.627			
	SOL	£17,763	10.785	£17,763	0.158	£112,401
20/40/40 SOL dose split	SC	£0	10.675			
	SOL	£24,055	10.897	£24,055	0.222	£108,295
Time horizon: 1 year	SC	£0	0.300			
	SOL	£968	0.308	£968	0.007	£133,088
Time horizon: 5 years	SC	£0	2.475			
	SOL	£6,638	2.528	£6,638	0.053	£125,661
Compliant patients	SC	£0	10.482			
	SOL	£18,795	10.627	£18,795	0.145	£129,839
Non-compliant patients	SC	£0	10.911			
	SOL	£22,293	11.155	£22,293	0.244	£91,508
50% compliant / 50% non-compliant	SC	£0	10.697			
	SOL	£20,544	10.891	£20,544	0.194	£105,795
Loss of response in SC arm (1.5 x base-case values)[1]	SC	£0	10.541			
	SOL	£19,978	10.810	£19,978	0.268	£74,421
Loss of response in SC arm (2 x base-case values)[1]	SC	£0	10.465			
	SOL	£19,978	10.810	£19,978	0.344	£58,039

SC: standard care; SOL: solriamfetol combination.

[1] The base-case values for the first and subsequent years were estimated as weighted averages of the treatment discontinuation rates due to loss of response in the solriamfetol arms (37.5 mg, 75 mg and 150 mg).

Source: Produced by ERG from an adapted version of the Company's model

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 obstructive sleep apnoea [ID1499]

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 Monday 3 August 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 Model population description

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
P12, Issue 2, Table - Row 2 "The mean baseline ESS ([redacted]) in the company's base case model is increased by the use of IPD for people with ESS>10 (rather than ESS≥10 as in the TONES 3 trial population). "	Amend to: "The mean baseline ESS ([redacted]) in the company's base case model is increased (from an overall baseline mean ESS of [redacted]) by the use of IPD for people with ESS>10 (rather than ESS≥10 as in the TONES 3 trial population).	For balance, the mean baseline ESS in the overall population (per CS Table 25) should be included, to allow comparison between that value and the value used in the base case model population.	Not a factual error, no change made
P12, Issue 2, Table – Row 2 "The mean baseline ESS ([redacted]) in the company's base case model is increased by the use of IPD for people with ESS>10 (rather than ESS≥10 as in the TONES 3 trial population). The company argue that this is "broadly consistent" with the European marketing authorisation for	We would like the statement "but do not give a clear justification for this restriction" to be amended as the justification for this exclusion is provided in the CS.	The justification for exclusion of the small proportion of patients with ESS=10 is provided on p127 and p118 of the CS – these patients had normal ESS scores therefore did not have EDS and were excluded from the model. Per CS p118, paragraph 2: In the UK, ESS scores ≤10 are considered 'normal' daytime sleepiness, thus in clinical practice, patients with OSA would usually have ESS scores substantially in excess of 10 at treatment initiation. The eligibility criteria for TONES 3 included patients with ESS scores ≥10, thus a small proportion of patients had	We agree that the CS includes an argument for defining EDS as ESS>10 on page 118, with additional references cited in Table 6. For clarity, we have amended the text on page 12 as below: "The company argues that ESS=10 falls within the range considered normal in UK clinical practice (CS Table 6 and page 118)."

solriamfetol which defined EDS as ESS≥10, **but do not give a clear justification for this restriction**"		normal ESS values at baseline (ESS=10): solriamfetol 37.5 mg, 5.4%; solriamfetol 75 mg, 5.2%, and solriamfetol 150 mg, 7.8%. To remove the variation between the clinical criteria for EDS (ESS≤10) and the patients in the trial (ESS≥10), all cost-effectiveness analyses were conducted using IPD and patients with baseline ESS=10 were excluded such that the trial populations would more accurately reflect UK practice.	
P12, Issue 2, Table – Row 2 "The company argue that this is "broadly consistent" with the European marketing authorisation for solriamfetol which defined EDS as ESS≥10."	The company argue that this is "broadly consistent" with the populations in trials supporting the European marketing authorisation for solriamfetol (i.e. the TONES trials), in which the patients had EDS defined as ESS≥10. This issue is also raised on p99, Table 34, Row 3 (ERG comments).	We would like this statement amended for clarity. The term 'broadly consistent' has been taken out of context of the original sentence, and as currently presented, it may incorrectly suggest an ESS score is defined within the marketing authorisation for solriamfetol. The original text per CS p126 was 'This is consistent with the population defined in the NICE scope and broadly consistent the TONES trials, and the European marketing authorisation of solriamfetol, both of which defined EDS as ESS ≥10.' This statement in the CS was demonstrating that the populations in the NICE scope (EDS, i.e. ESS>10) and those	This is not a factual error. The electronic medicines compendium (emc) for solriamfetol states the following with respect to the pivotal trials: "For entry into both studies, patients had to have excessive daytime sleepiness (ESS score ≥10)." However, for simplicity we have amended as above. https://www.medicines.org.uk/emc/product/11016/smpc

		in the TONES trials, which in turn supported the EMA application (ESS≥10) were not identical, but were broadly consistent, as only a small number of patients in the TONES trials had an ESS=10. The EMA itself does not stipulate an ESS score that defines EDS in either the OSA or narcolepsy indication for solriamfetol.	
P12, Issue 2 – Table, Row 2 "Restriction to a population with more severe EDS is likely to enhance effectiveness, and hence cost-effectiveness of solriamfetol."	We request that this statement is amended as it incorrectly states that the CS restricted the analysis to a more severe EDS. A similar statement is made on ERG report p70, final line.	Per CS p118, patients with ESS=10 are considered to have normal levels of sleepiness. Therefore, the exclusion of ESS=10 from the CS analysis did not restrict the severity of EDS, as those patients with ESS=10 would not be considered to have EDS in UK clinical practice.	Not a factual error, but for clarity we have amended this sentence here (and on page 71, ERG report 4.2.3.2) as below. "Restriction to a population with ESS>10 is likely to enhance effectiveness, and hence cost-effectiveness of solriamfetol."

Issue 2 Treatment response, scenario ICER

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
P13, Issue 3, Table – Row 4 "With a response definition of ESS reduction of 2 or more points, the company's base case ICER increases above £30,000 per QALY"	Amend to: "With a response definition of ESS reduction of 2 or more points, the company's base case with ERG corrections pushed the ICER above £30,000 per QALY (compared with the ICER of £29,484 in the original CS scenario analysis for ESS reduction of 2 or	The original language in the report implies that this analysis was the company's base case as originally submitted to NICE, and not the base case with ERG corrections. Further, for balance, the new statement includes the original CS ICER for this scenario.	We agree that we should have specified that this scenario includes ERG corrections (as below). However, in the absence of arguments that those corrections are wrong, it is not necessary to cite the original CS ICER for this

	more.)"		scenario. "With a response definition of ESS reduction of 2 or more points, the company's base case ICER **with ERG corrections** increases above £30,000 per QALY."

Issue 3 Treatment discontinuation rates

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
P16, Issue 7, Table Row 2 "The company report that solriamfetol treatment discontinuation due to treatment emergent adverse events (TEAEs) and loss of response in the TONES 3 and 5 trials was dose dependent. However, the modelled rates in the company base case are the same across all solriamfetol doses"	Amend to: "The company report that solriamfetol treatment discontinuation due to treatment emergent adverse events (TEAEs) and loss of response in the TONES 3 and 5 trials was dose dependent. Although the modelled rates in the company base case are the same across all solriamfetol doses, the company has conservatively applied the highest rate of discontinuations due to TEAEs from TONES 5 (which included the unlicensed 300 mg dose) to all arms. They also applied the rate of discontinuation due to loss of response observed in TONES 5 although there were [redacted] discontinuations due to loss of response in the placebo-controlled TONES 3 trial."	For balance, the statement should reflect that although the rates applied were the same, these were the highest rates available from TONES trial data. Per CS p147, [redacted] patients in TONES 3 discontinued due to loss of response, but the CS included the loss of response data from TONES 5 and used the higher rate of TONES 5 discontinuation due to AEs available.	Not a factual error, no change made We believe that the assumptions made in the model should be consistent with the relevant clinical evidence from the pivotal trial and TONES 5 follow up. As we note, modelling of dose-dependent loss of response and TEAEs is important because of uncertainty over the dose-split in clinical practice. Please also note that this is the executive summary, and further information about the company's approach is provided in the cross-referenced section

			4.2.6.4 of the ERG report.

Issue 4 Impact of adverse events leading to hospitalisation

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
P17, Issue 8, Table – Row 2 "We note that a proportion of serious adverse events (SAEs) in TONES 3 led to hospitalisation [redacted]."	Amend to: "We note that a proportion of serious adverse events (SAEs) in the 150 mg arm of TONES 5 led to hospitalisation [redacted]."	Based on Table 28, p93 of the ERG report, this appears to be referring to the 150 mg arm of the TONES 5 trial thus these points should be clarified/corrected. Please note further correction and clarification is sought by Jazz on this value in Issue 26.	Clarified and corrected, thank you.

Issue 5 Background Section

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
P20, Bullet point 1 "**Moderate to severe OSA** requires additional interventions, the most widely used of which in the UK is positive airway pressure (PAP) / continuous positive airway pressure (CPAP). NICE guidance TA139 (2008) recommends CPAP for adults with moderate or severe symptomatic obstructive sleep apnoea hypopnoea syndrome	We would request that NICE guidance is presented as an independent bullet point, as shown below: • **Moderate to severe OSA** requires additional interventions, the most widely used of which in the UK is positive airway pressure (PAP) / continuous positive airway pressure (CPAP). • NICE guidance TA139 (2008) recommends CPAP for adults with moderate or severe symptomatic obstructive sleep apnoea hypopnoea syndrome (OSAHS), or as a treatment	For balance, the NICE guidance from TA139 could be presented as a separate bullet point. As currently shown, it suggests that TA139 only applies to moderate/severe OSA whereas there is guidance on mild OSA.	Not a factual error but change made as requested.

(OSAHS), or as a treatment option for adults with mild OSA if their symptoms adversely affect their quality of life and daily activities."	option for adults with mild OSA if their symptoms adversely affect their quality of life and daily activities.		
P20, Paragraph 1, EDS "People with EDS experience periods of tiredness during the day"	Amend to: "People with EDS experience periods of extreme and overwhelming sleepiness during the day,"	The level of sleepiness experienced by patients with OSA is not accurately described by 'tiredness'. Tiredness may occur in any individual but does not cause them to fall asleep whilst e.g. eating or in the bathroom (per CS p18 paragraph 1).	We do not regard this as a factual error. The sleepiness/tiredness may not necessarily be extreme and overwhelming given the fact EDS severity can be classified as mild, moderate or severe. However, we have replaced the term tiredness with sleepiness, and the sentence now reads "People with EDS experience periods of sleepiness during the day of varying extremity"
P20, Paragraph 2, EDS description "The CS notes that optimal management of OSA can reduce symptoms related to the condition itself (e.g. apnoeic/hypopnoeic episodes), as well as EDS (e.g. dozing during the day)."	Amend to: "The CS notes that optimal management of OSA can reduce symptoms related to the condition itself (e.g. apnoeic/hypopnoeic episodes), as well as EDS (e.g. extreme and irresistible sleepiness)."	The level of sleepiness experienced by patients with OSA is not accurately described by 'dozing during the day'. Dozing during the day may occur in any individual but these people do not have levels of tiredness that cause them to doze off whilst eating or in the bathroom, nor do they need to 'plan their day around their EDS' (CS p18 paragraph 1)	Not a factual error, no change made. The ESS asks patients to score their likelihood of "*dozing* off or falling asleep" in a variety of day to day situations.

P21, Last paragraph "However, the ERG's understanding, informed by expert clinical opinion and the literature, is that primary OSA therapy can alleviate EDS symptoms (NB. EDS as measured by the Epworth Sleepiness Scale was the key clinical effectiveness outcome measure that informed the analysis underpinning NICE's recommendation of CPAP for OSAHS – NICE TA139)."	Amend to: "However, the ERG's understanding, informed by expert clinical opinion and the literature, is that primary OSA therapy can alleviate EDS symptoms. Although primary OSA therapy (including CPAP) may resolve EDS in some patients, they are not specifically indicated to manage EDS, and for patients whose EDS is not satisfactorily reduced by primary OSA therapy, these patients continue to experience the burden of their EDS. (NB. EDS as measured by the Epworth Sleepiness Scale was the key clinical effectiveness outcome measure that informed the analysis underpinning NICE's recommendation of CPAP for OSAHS – NICE TA139)"	For balance, and per CS p133, paragraph 1, we feel it is important to state that primary OSA therapies are not indicated to treat EDS and that they do not resolve EDS in all patients, or may not resolve EDS fully in some patients".	Not a factual error, no change made. Our clinical experts are of the opinion that primary OSA therapies such as CPAP *are* indicated to manage EDS resulting from OSA. In many other places in our report we have made it explicit that EDS may not resolve fully in some patients.
P21, Last paragraph "Discordance between OSA severity and EDS severity occurs in patients who are benefitting from optimal primary OSA therapy but who experience residual EDS"	Amend to: "Discordance between OSA severity (i.e. AHI scores) and EDS severity occurs in patients with OSA and EDS, including patients who are benefitting from optimal primary OSA therapy but who experience residual EDS"	Discordance between OSA severity (AHI) and EDS severity is not restricted to patients who are "benefitting from optimal primary OSA therapy" – this could be the case in any patient with OSA, diagnosed or undiagnosed, and with or without EDS. Per CS p14, final paragraph, p15, paragraph 2, and p16, final paragraph - Some patients with OSA are unaware of their condition, and/or unaware of their night-time symptoms but may experience EDS. Alternatively, they may be untreated, and undiagnosed because they do not experience	Amended as requested

		EDS. As such, the discordance between OSA and EDS can exist across all patient with OSA.	
P21, Last paragraph "Discordance between OSA severity and EDS severity occurs in patients who are benefitting from optimal primary OSA therapy but who experience residual EDS. It is this group of patients who require independent (additional) treatment to reduce sleepiness and improve wakefulness (the ability to remain awake and alert). "	Amend to: "Discordance between OSA severity and EDS severity occurs in patients who are benefitting from optimal primary OSA therapy but who experience residual EDS. It is the subgroup of patients whose EDS is not satisfactorily managed by a primary OSA therapy who require treatment to reduce sleepiness and improve wakefulness (the ability to remain awake and alert)"	The target population for solriamfetol is not restricted to those patients with a discordance between EDS and OSA severity who are benefitting from optimal primary OSA therapy but who experience residual EDS. The licensed indication for solriamfetol is to improve wakefulness and reduce EDS in adult patients with OSA whose EDS has not been satisfactorily treated by primary OSA therapy, such as continuous positive airway pressure. As such, there are additional patients who would also be eligible for solriamfetol other than those who have mismatched OSA and EDS severity, and are benefitting from optimal primary OSA therapy but who experience residual EDS.	Amended as requested

Issue 6 Solriamfetol dosing

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
P22, Final paragraph "Solriamfetol is orally administered once daily, and is available in doses of 37.5 mg, 75 mg, and 150 mg. The recommended starting dose is 37.5 mg which can be titrated up to a maximum dose of 150 mg"	Amend to: "Solriamfetol is orally administered once daily, and is available in doses of 37.5 mg, 75 mg, and 150 mg. The recommended starting dose for patients with OSA is 37.5 mg which can be titrated at intervals of at least 3 days, up to a maximum dose of 150 mg"	These edits are consistent with the SmPC for solriamfetol, highlighting the minimum titration intervals required.	Amended as requested

Issue 7 CPAP compliance rates

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
P23, First paragraph under table "The ERG's clinical experts commented that they would expect patients to demonstrate good compliance with their primary OSA therapy to be considered for solriamfetol treatment. They estimate that between 20% and 70% of patients are compliant." A compliance rate of 50% is mentioned in Table 5, p33, Table 34, p99, and Appendix 9.5	We request that one value or range of CPAP compliance is used throughout the report.	A compliance rate of 50% is mentioned in Table 5, p33, Table 34, p99, and Appendix 9.5 (Table) which is inconsistent with the 20–70% range reported on p23. For consistency it would be helpful to use the same value or range throughout.	We have amended the sentence to say: "The ERG's clinical experts note that compliance to primary OSA therapy varies between patients, and that they would expect patients to demonstrate good compliance to be considered for solriamfetol treatment"

Issue 8 ERG background conclusion

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
P24, final paragraph "The CS provides a detailed description of the characteristics of EDS in OSA. The CS provides an adequate justification for the place of solriamfetol as a treatment for residual EDS in addition to on-going primary OSA therapy"	Amend to: "The CS provides a detailed description of the characteristics of EDS in OSA. The CS provides an adequate justification for the place of solriamfetol as a treatment for residual EDS patients with OSA whose EDS has not been satisfactorily treated by primary OSA therapy, such as continuous positive airway pressure"	This amendment is consistent with the licensed indication for solriamfetol.	Amended as requested

Issue 9 Trial characteristics

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
P29, Paragraph 1, TONES 3 "**TONES 3** is the pivotal phase III RCT which supported the company's EMA licence application"	Amend to: "**TONES 3** is the pivotal phase III RCT in patients with EDS due to OSA, which supported the company's EMA licence application"	To clarify that TONES 3 was the pivotal trial for EDS in OSA as there was another pivotal trial in the EMA licence application (TONES 2, narcolepsy).	Text clarified as suggested.

Issue 10 Table 4, Characteristics of the TONES trials

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
P30, Table 4, Row 3, Population (TONES 4) "Mean sleep latency ≤30 minutes"	Amend to: "Mean sleep latency <30 minutes"	The mean sleep latency for TONES 4 entry was <30 minutes.	Error corrected, thank you.

P30, Table 4, Row 4, Intervention (TONES 4) "Solriamfetol 75 mg initiated (2 weeks) and then titrated to and stabilised at maximum tolerated dose (75 mg, 150 mg or unlicensed 300 mg) (2 weeks). Then randomised withdrawal to solriamfetol (75 mg, 150 mg or 300 mg) or placebo (2 weeks)"	Amend to: "Solriamfetol 75 mg is initiated and then titrated up or down to a maximum tolerated dose (75 mg, 150 mg or unlicensed 300 mg) (2 weeks), followed by a stable dose phase with solriamfetol continued at this stable dose (2 weeks). Then randomised withdrawal to solriamfetol (75 mg, 150 mg or 300 mg) or placebo (2 weeks)."	The study design description was incorrect; titration only occurred during the first 2 weeks, and patients continued .	Description has been corrected.
P30, Table 4, Row 4, Intervention (TONES 5) "Solriamfetol (combined dose arm: 75, 150 or unlicensed 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"	Amend to: "Solriamfetol (combined dose arm: 75, 150 or unlicensed 300 mg once daily); patients started on solriamfetol 75 mg 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. Then a maintenance phase (up to 52 weeks) during which up to 3 dose adjustments were allowed within the first 12 weeks. "	This amendment provides a clearer description of the study design	Although not a factual error the description has been amended to provide more information.
P31, Table 4, Row 9, Number of centres Numbers are missing AiC mark up	For TONES 4 and 5, the number of centres are AiC [redacted](US, Finland France, Germany and Sweden) | [redacted])	AiC mark up missing. Note the AiC mark up for TONES 5 was incorrectly omitted from the CS. This will be updated in final redacted versions.	The ERG has updated the text to show AiC marking that was missing from the CS.
P31, Table 4, Row 10, UK centres	TONES 5 number of UK centres is AiC	The locations of TONES 5 are AiC. Note the AiC mark up for	The ERG has updated the text to show AiC marking that was missing from the

		TONES 5 was incorrectly omitted from the CS. This will be updated in final redacted versions.	CS.

Issue 11 Patient baseline characteristics

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
P32, Section 3.2.3.2, Paragraph 1 "Participants from these trials formed the subgroup of participants with OSA in TONES 5 and the baseline characteristics of participants in TONES 5 (CS Table 8) reflects this"	Amend to: "Participants from these trials formed a proportion of the subgroup of participants with OSA in TONES 5 and the baseline characteristics of participants in TONES 5 (CS Table 8) reflects this"	Patients with OSA from TONES 3 and 4 were not the only patients with OSA enrolled in TONES 5 – a small proportion came from other studies.	The ERG has amended the text to show that the majority of the participants ([redacted]) in TONES 5 came from TONES 3 and TONES 4.
P32, Table 5, Row 7, ESS score "Baseline ESS scores were approximately 15 (range 14.8 to 15.6)."	Amend to: "Mean baseline ESS scores were approximately 15 (range of mean ESS scores across arms were 14.8 to 15.6)"	This edit more accurately reflects that these ESS scores were means, and across arms (as opposed to the range of individual ESS scores within one trial).	Text amended to improve clarity as suggested.

Issue 12 Risk of bias assessment

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
P35, Paragraph 1, TONES 3 "In TONES 3, overall, 12% of the mITT population did not	Amend to: "In TONES 3, overall, 12% of the mITT population did not complete the study. The	AiC mark up was missing from the report	AIC mark up added

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
complete the study. The percentage of patient withdrawals in the mITT population varied between the placebo, 37.5 mg, 75 mg, 150 mg and 300 mg dose arms (11%, 13%, 7%, 9% and 18% respectively). A higher proportion of withdrawals was observed in the unlicensed 300 mg dose arm chiefly because of a higher incidence of withdrawals due to adverse events (AEs) in this arm (n=13 vs n=0-4 across the other arms). Within the licensed dose arms, there was no evidence of any systematic reason for imbalances in drop-out rates between trial arms. Lack of efficacy was not reported as a reason for withdrawal in any solriamfetol arm. The ERG conclude that it is unlikely that the slight imbalance in withdrawals between groups would cause a significant risk of bias”	percentage of patient withdrawals in the mITT population varied between the placebo, 37.5 mg, 75 mg, 150 mg and 300 mg dose arms ([redacted] and [redacted] respectively). A higher proportion of withdrawals was observed in the unlicensed 300 mg dose arm chiefly because of a higher incidence of withdrawals due to adverse events (AEs) in this arm (n=[redacted] vs n=[redacted] across the other arms). Within the licensed dose arms, there was no evidence of any systematic reason for imbalances in drop-out rates between trial arms. Lack of efficacy was not reported as a reason for withdrawal in any solriamfetol arm. The ERG conclude that it is unlikely that the slight imbalance in withdrawals between groups would cause a significant risk of bias”		
P35, Paragraph 2, TONES 3 “For the secondary outcomes of the Patient and Clinician Global Impression of Change scores (PGI-c and CGI-c, see section **Error! Reference source not found.**, only	Amend to: “For the secondary outcomes of the Patient and Clinician Global Impression of Change scores (PGI-c and CGI-c, see section **Error! Reference source not found.**, only single rather than multiple imputation methods were used, however	AiC mark up was missing from the report	AIC mark up added

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
single rather than multiple imputation methods were used, however the most conservative of these methods (assuming worst case scenario for missing values; TONES 3 CSR Section 11.4.1.3.2.) produced similar results to the primary analysis (which used the last-observation carried forward (LOCF) method). “	the most conservative of these methods (assuming worst case scenario for missing values; TONES 3 CSR Section 11.4.1.3.2.) produced similar results to the primary analysis (which used the [redacted] method). “		
P36, Sub-bullet 2, Expert prescribing “A second expert thought it possible that the 75 mg dose may be used as a starting dose particularly once clinical experience is gained prescribing solriamfetol in practice”	Amend to: “A second expert thought it possible that the 75 mg dose may be used as a starting dose particularly once clinical experience is gained prescribing solriamfetol in practice. (Note that this is not a recommended starting dose for solriamfetol in the OSA SmPC)”	For balance, the report should state that this is not the recommended starting dose for solriamfetol in the OSA indication.	Text updated as suggested.

Issue 13 Outcomes assessment section

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
P40, TONES 5 study, Table 9, Footnote B “[b] minimally, much or very much improved or greater”	Amend to: “[b] minimally, much or very much improved”	Per CS Table 6, PGI-c ratings do not include an ‘or greater’ score so this edit removes that text	Text amended as suggested

Issue 14 Results of the clinical effectiveness studies

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
P44, Results Section 3.2.6.1 "In this section we report on the primary outcomes and selected secondary outcomes from the TONES 3, TONES 4 and TONES 5 trials. "	Amend to: **"**In this section we report on the primary outcomes and selected secondary outcomes from the TONES 3, TONES 4 and TONES 5 trials. Note that data presented for TONES 5 results are for the subgroup of patients with OSA only"	It is not clear from the ERG report that the results are specific to those patients with OSA (and excluded patients with narcolepsy)	Text amended as suggested
P46, TONES 3 post-hoc ESS The final value, of the final line "(37.5%)"	Value corrected to "(37.7%)"	The correct value for normalisation of ESS score for placebo is 37.7%	Corrected
P47, TONES 5: ESS Results from open-label phase "Improvements in ESS were observed from week 2 of treatment for both solriamfetol doses and were maintained over time"	Amend to: "In both group A and group B, the improvements in ESS were observed from week 2 of treatment for both solriamfetol doses and were maintained over time".	The current text is not clear that these results apply to both groups in TONES 5 (whereas the following bullet point, specifies the results for each group)	Text amended as suggested
P49, TONES 3 secondary MWT endpoints "Compared to placebo, statistically significant differences in the change in ESS from baseline "	Amend to: "Compared to placebo, statistically significant differences in the change in MWT from baseline "	ESS is incorrectly stated, this refers to MWT results	Corrected
P49, TONES 4 and TONES 5: MWT "In keeping with the analysis of ESS scores, patients switching to placebo had a greater deterioration in MWT (-12.1 minutes) compared to	Amend to: "In keeping with the analysis of ESS scores, patients switching to placebo had a greater deterioration in MWT (-12.1 minutes) compared to those remaining on solriamfetol (-1.0 minutes) in TONES 4 during the randomised withdrawal phase"	Although the heading states the phase, for clarity this edit reiterates this within the results statement	Text amended as suggested

<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>those remaining on solriamfetol (-1.0 minutes) in TONES 4 “</td><td></td><td></td><td></td></tr>
<tr><td>P51, Table 19, TONES 4

N numbers and row title are inaccurate</td><td>Corrections to the n numbers, values and row title (in red):
<table><tr><td rowspan="2">Study (endpoint)</td><td colspan="4">Change from baseline in:</td></tr><tr><td colspan="2">Percentage of nights of primary OSA therapy usage</td><td colspan="2">Average no. of hours per night of primary OSA therapy usage</td></tr><tr><td>Placebo [redacted]**)</td><td>Solriamfetol, all doses [redacted]**</td><td>Placebo [redacted]</td><td>Solriamfetol, all doses [redacted]</td></tr><tr><td>TONES 4 (mean change from start to end of randomised withdrawal phase)</td><td>*[redacted]</td><td>*[redacted]</td><td>[redacted]</td><td>[redacted]</td></tr></table></td><td>The n numbers provided were inaccurate (per CSR Table 21, p92) and the row title did not specify that these were mean values. Positive values added to the percentage of nights for clarity that these were mean increases.</td><td>Corrected. In addition, the ERG has corrected the cross reference in the Table footnote which now correctly states ‘CS Section B.2.6.3.7’</td></tr>
</table>

Issue 15 Subgroup analysis conclusion/summary

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
P55, Bullet point 1, under the table "For ESS, a similar degree of improvement was seen in both subgroups for the comparison between solriamfetol 150 mg and placebo. Although there was a numerical difference in the degree of improvement between subgroups for the 37.5 mg and 75 mg doses, this may reflect random variation because the numbers of patients were smaller in these groups (37.5 mg arm compliant n=39, non-compliant n=17; 75 mg arm compliant n=42, non-compliant n=16)."	Amend to: "For ESS, a similar degree of improvement for the comparison between solriamfetol 150 mg and placebo was seen in the compliant and non-compliant subgroups (-4.2 and -5.0 respectively). The degree of improvement was not as similar for the compliant and non-compliant subgroups for the comparison between solriamfetol 75 mg (-1.3 and -2.6) and 37.5 mg doses (-2.4 and -0.7) and placebo, however this may reflect random variation because the numbers of patients were smaller in these groups (37.5 mg arm compliant n=39, non-compliant n=17; 75 mg arm compliant n=42, non-compliant n=16)."	The original text made it unclear that the results summarised were referring to the relative comparability of the ESS reductions in the two subgroups, (as opposed to the significance values between the solriamfetol doses and placebo within each subgroup). The amended text makes it clear that the comparisons are being made between the relative reduction in ESS within each dose arm, but between the compliant vs non-compliant groups.	Although not factually incorrect the ERG has amended the text as suggested for clarity.

Issue 16 Safety outcomes

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
P56, Paragraph 3, TONES 5 "The ERG notes that long-term safety data from TONES 5 for the licensed solriamfetol doses (75 mg and 150 mg only, the 37.5 mg dose was not included in TONES 5) in patients with OSA is limited	Amend to: "The ERG notes that long-term safety data from TONES 5 for the licensed solriamfetol doses (75 mg and 150 mg only, the 37.5 mg dose was not included in TONES 5) in patients with OSA is limited because only [redacted] patients received a modal dose of 75 mg and [redacted] patients	This amendment clarifies that the lack of data was due to the study design, titrating to maximum tolerated dose, and clarifies that although the maximum dose is unlicensed, solriamfetol was still well tolerated in the trial.	This is not a factual error, however the ERG has added the following text to this paragraph "This reflects the study design, which titrated patients to the maximum tolerated dose of solriamfetol"

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
because only [redacted] patients received a modal dose of 75 mg and [redacted] patients received a modal dose of 150 mg; the remainder ([redacted]) received the unlicensed 300 mg dose of solriamfetol. “	received a modal dose of 150 mg; the remainder ([redacted]) received the unlicensed 300 mg dose of solriamfetol. This was due to the study design, which titrated patients to the maximum tolerated dose of solriamfetol, however solriamfetol was well tolerated in TONES 5.“		
P56, Paragraph 3, TONES 5 “Mean (SD) treatment exposure in the OSA population was 248.7 ([redacted]) days ([redacted]) for all doses combined but less for the 75 mg dose ([redacted]) days) and 150 mg dose ([redacted] days).”	Amend to: “Mean (SD) treatment exposure in the OSA population was [redacted]) days ([redacted]) for all doses combined but less for the 75 mg dose ([redacted]) days) and 150 mg dose ([redacted] days).”	AiC mark up was missing from the exposure value.	AIC mark up added
P56, Paragraph 4, TONES 4 “In TONES 4, 37.4% of patients experienced AEs during the titration phase declining to 4.5% during the stable dose phase. Adverse event rates were higher in the patients in TONES 4 who were randomised to continue solriamfetol treatment (3.2%) compared with those who switched to placebo (1.6%). “	Amend to: “In TONES 4, [redacted] of patients experienced AEs during the titration phase declining to [redacted]% during the stable dose phase. Adverse event rates were higher in the patients in TONES 4 who were randomised to continue solriamfetol treatment ([redacted] compared with those who switched to placebo ([redacted]“	AiC Mark up was missing from these values	AIC mark up added; Cross referenced to CS table 22 also inserted.
P57, Table 22, Adverse events TONES 4, All doses combined	The company requests that an updated set of AE data for TONES 4 is provided in this table.	For balance, the company feels that Table 22 in its current form presents the TONES 4 AEs out of context and instead the overall	Table 22 data updated with figures from CSR Table 26. All have therefore been marked as

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
		rates of AEs for TONES 4 across all phases from CSR Table 26, p102 should be provided in order to be comparable with the data presented here for TONES 3 and 5. Although the original CS presented AEs across each phase, the data presentation format varied for the submission, thus all AEs by phase were shown for transparency.	CIC. The ERG has also amended the footnote to Table 22 of the ERG report to reflect this update.
P58, Table 23, Row 4, CV events "Nine serious cardiovascular events were observed in TONES 5 of which 6 occurred at the unlicensed 300 mg dose. Two of the 9 serious events (i.e. cerebrovascular accident at the 150 mg dose and atrial fibrillation at the 300 mg dose) were considered related to study drug."	Amend to: "[redacted]serious cardiovascular events were observed in TONES 5 of which 6 occurred at the unlicensed 300 mg dose. [redacted]of the [redacted] serious events (i.e. cerebrovascular accident at the 150 mg dose and atrial fibrillation at the 300 mg dose) were considered related to study drug."	AiC mark up was missing from these values for CV events.	AIC mark up added
P59, Table 23, Row 4 title/label: CV events requires a footnote "Cardiovascular events, increased blood pressure and increased heart rate"	Amend to: Row 4 title: "Cardiovascular events, increased blood pressure* and increased heart rate" Footnote text: "* includes reports of blood pressure increased, hypertension, and procedural hypertension "	To be consistent with the presentation of depression/suicidal ideation within this table, we suggest a footnote is added for increased BP Note we have denoted the footnote with * as this edit requires the footnote sequence to be amended accordingly	Footnote added as requested

Issue 17 Section 4.1 intro paragraph

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
P62, S4.1, paragraph 1 "An overview of the key assumptions of the economic analyses submitted for TA130 is presented in CS Table 24"	Amend to: "An overview of the key assumptions of the economic analyses submitted for TA139 is presented in CS Table 24"	Correction of a typo in the NICE TA number	Corrected, thank you.

Issue 18 Model Structure

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
P66, First line "As for non-responders, it is assumed that ESS for patients who discontinue solriamfetol returns immediately to baseline ESS."	Amend to: "As for non-responders, it is assumed that ESS for patients who discontinue solriamfetol returns immediately to baseline ESS (i.e. their ESS on standard of care)".	This edit clarifies that patients do not return to their untreated/pre-treatment ESS score but rather the ESS score they would achieve on standard of care.	Clarified.

Issue 19 Section 4.2.3 Population

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
P71, Paragraph 2 "In TONES 3, 92% of patients who received solriamfetol had used or were using CPAP at baseline. It is not clear to what extent this reflects current UK practice"	Amend to: "In TONES 3, 92.7% of patients who received solriamfetol had used or were using PAP at baseline. It is not clear to what extent this reflects current UK practice"	There was a typo in the value, and the type of PAP is not specified in TONES 3.	Corrected. "In TONES 3, 92.7% of patients who received solriamfetol and had reported current or prior use of a primary OSA therapy were using PAP at baseline (CS B.2.3.2.1.1). Overall, 70% of the TONES 3 safety

			population were compliant with PAP at baseline (CS Table 7). It is not clear to what extent this reflects current UK practice."
P71, paragraph 3 "In addition to the question of baseline CPAP compliance, there is uncertainty over potential changes in CPAP compliance over time associated with the use of solriamfetol"	Amend to: "In addition to the question of baseline CPAP compliance, there is uncertainty over potential changes in CPAP compliance over time associated with the use of solriamfetol. However the company completed an exploratory analysis that showed compliance was not significantly affect by solriamfetol treatment"	This edit was made for balance, as the exploratory analysis of the trial population showed CPAP compliance was not impacted	We agree that it is appropriate to reference this exploratory analysis and have also added a cross-reference to the ERG critique. "In addition to the question of baseline CPAP compliance, there is uncertainty over potential changes in CPAP compliance over time associated with the use of solriamfetol. The company reported an exploratory analysis that showed that changes in use of primary OSA in TONES 3 were small and similar for solriamfetol and placebo arms (CS B.2.6.1.8). See section 3.2.6.1.4 above for ERG critique of this analysis"

Issue 20 Section 4.2.4 Interventions

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
P71, S4.2.4, first line	Amend to:	The comparator in the NICE scope	Clarified as suggested

“The intervention in the company’s analysis is solriamfetol in addition to primary OSA therapy (as described in section **Error! Reference source not found.** above). “	“The intervention in the company’s analysis is solriamfetol in addition to established clinical management (as described in section 2.2.3 above). “	was established clinical management without solriamfetol, i.e. the ongoing/continued/existing standard of care being received by the patient before they are prescribed solriamfetol. The licensed indication is to improve wakefulness and reduce EDS in adult patients with OSA whose EDS has not been satisfactorily treated by primary OSA therapy, such as continuous positive airway pressure. As such a patient may have previously attempted CPAP but their EDS not been satisfactorily managed.	

Issue 21 Comparison of TONES 3 ESS effects Table

<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>P73, Table 26, Final Section, Company Base Case, Last 5 rows

The company base case section contains multiple errors</td>
<td>Edits to the table rows are presented in red font
<table>
<tr><th colspan="5">IPD analysis with centring ESS>10 (company base case)</th></tr>
<tr><td>ΔESS difference relative to placebo</td><td>-</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td></tr>
<tr><td>Proportion of responders (ΔESS ≥3)</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td></tr>
<tr><td>Mean ESS for responders</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td></tr>
<tr><td>Mean ESS for non-responders</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td></tr>
</table>
</td>
<td>There were some typographical errors in the table results presented. Based on the raw IPD provided, the values are as presented in this updated table.</td>
<td>We have corrected the values for ΔESS relative to placebo. Note that the correct values for this scenario are: -1.5, -1.2 and -4.4 respectively for sol doses 37.5, 75 and 150 mg. (see sheet _IPD_OSA_Summary in the submitted model).

The value for standard care ‘responders’ is not an error: this is included for comparison with the non-centred analyses.

For clarity we have also added a footnote to this table citing our sources.</td>
</tr>
</table>

Issue 22 Adjustment for placebo-arm response ('centring')

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
P75, final line, bullet IV "Changes over time for patients withdrawn from treatment in the TONES 4 discontinuation trial who subsequently restarted treatment in the TONES 5 maintenance trial."	Amend to: "Changes over time for patients withdrawn from treatment in the TONES 4 trial who subsequently restarted treatment in the TONES 5 maintenance trial, after a break in treatment of unknown duration between TONES 4 and TONES 5."	The edited text provides further detail about this population of patients and removes the statement that TONES 4 was a discontinuation trial (TONES 4 was a randomised withdrawal trial).	We have deleted the word 'discontinuation'. Additional information about the gap between TONES 4 and 5 is not necessary here.
P76, First paragraph "MWT is a more objective test than ESS, and there are clear differences in changes over time in the TONES 3 placebo arm between ESS (CS Figure 5) and MWT (CS Figure 6): MWT does not change through the 12-week follow up; whereas ESS falls in week 1 and maintains this reduction through to week 12"	Amend to: "MWT is a more objective test than ESS, and there are clear differences in changes over time in the placebo arm of TONES 3, between the ESS (CS Figure 5) and MWT (CS Figure 6): For the placebo arm, the MWT score does not change through the 12-week study; whereas the ESS score falls in week 1 and maintains this reduction through to week 12"	This edit clarifies that this text is specific to the placebo arm only (as these results are not mirrored in the solriamfetol arms.)	This is not an error, no change made.
P76, Paragraph 2 "We note however, that MWT and ESS do measure different (though obviously related) concepts. ESS measures EDS (likelihood of dozing) in different day to day contexts, recalled over a 7-day period by patient self-report. "	Amend to: "We note however, that MWT and ESS do measure different (though obviously related) concepts. ESS measures EDS (likelihood of dozing) in different day to day contexts, recalled over a [redacted] period by patient self-report. "	AiC mark up for the duration was missing.	AiC added

Issue 23 4.2.6.4 Discontinuation

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
P77, final paragraph "but the same rate of 3.6% is applied in the first and consecutive years across the solriamfetol treatment arms "	Amend to: "but the same rate of [redacted]% is applied in the first and consecutive years across the solriamfetol treatment arms "	AiC mark up on this value was missing	Corrected, thank you.

Issue 24 EQ-5D

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
P80, First paragraph "although mean differences versus placebo were only significant for the solriamfetol 150 mg dose (CS Table 14). In contrast, the EQ-5D Index score improved across all arms in the first week, but there were no consistent trends over 12 weeks"	Amend to: " although mean differences versus placebo were [redacted] (CS Table 14). In contrast, the EQ-5D Index score improved across all arms in the first week, but there were no consistent trends over 12 weeks"	Significant values for these results are not publicly available so we have added the AiC mark up	AiC added

Issue 25 ERG conclusion on drug acquisition costs

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
P91, First paragraph "We believe that the company's deterministic sensitivity analyses for the proportions of patients taking 37.5 and 75 mg solriamfetol doses (see section 5.2.1) are implemented incorrectly because the total 'share' of doses in those analyses is not equal to 100%."	We would like the ERG to amend this statement in line with our justification provided.	The company analysis was set up to automatically adjust the total share of doses to 100%. As outlined on CS p181, paragraph 1, bullet point 3, "the proportion of patients on 150 mg changes to ensure all three doses total to 100%"	This statement has been deleted.

Issue 26 Table 28 in the ERG Report

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
P92, Table 28, Hospitalisation due to AEs, solriamfetol 150 mg "[redacted]"	Jazz seek clarification text to be added on the data points provided for hospitalisation due to serious AEs. This issue is also noted for	It is unclear how the n=[redacted] from [redacted] is derived from Appendix Table 40, as the number of unique patients is listed as [redacted] (based on unique ID number) and the number of individual AEs is [redacted]. If the ERG are modelling proportion of patients hospitalised as per the header of Table 28, then the value should more appropriately be [redacted], based on ERG table Appendix Table 40. If this value is retained by the ERG then the derivation of this value should be made clearer. Jazz would also take this opportunity to query the appropriateness of using this value since it adds costs to the solriamfetol arm but not to the comparator arm. Comparative data from TONES 3 (Placebo 2/119 (1.7%);	The title of Table 28 has been changed to "Estimated probability of hospitalisation per model cycle". The footnote to Table 28 has been amended as follows: "See **Error! Reference source not found. Error! Reference source not found.**. Note that some of the records in **Error! Reference source not found.** were for the same patients and their inpatient admissions were recorded on the same day. If more than one record was made for the same patient on the same date,

	Table 40, in the Appendix, which presents the related Hospitalisation due to AEs data.	Soriamfetol: 37.5 mg 2/58 (3.4%); 75 mg 0/62 (0%); 150 mg 1/117 (0.9%)) shows that there is no obvious difference between SAE rates between placebo and solriamfetol, nor an obvious dose dependent trend with solriamfetol. Furthermore none of the SAEs encountered in TONES 3 were deemed to be related or suspected to be related to solriamfetol, and similarly only 1 patient receiving licensed doses had an SAE in TONES 5 that was deemed as treatment related (Subject ID: [redacted]; solriamfetol 150 mg). On this basis Jazz would argue that it is inappropriate to model hospitalisation resulting from these SAEs as an additional cost over the standard of care arm.	only one instance of hospitalisation was modelled to avoid double-counting." According to the assessment report for TA139 NICE appraisal of CPAP for OSA (page 26), serious side effects of CPAP treatment are "thought to be very rare". We note that "a greater proportion of patients randomised to solriamfetol in TONES 3 had treatment-related AEs compared to placebo ([redacted]%) with [redacted] observed for 150 mg ([redacted]%) versus 75 mg ([redacted]%) and 37.5 mg ([redacted]%) during the first 12 weeks of treatment" (ERG report section 3.2.6.4). Regarding serious AEs in TONES 5, "[redacted]" (ERG report section 3.2.6.4). The company do not take into consideration the cost of managing treatment-related AEs although the AE rates in the solriamfetol arms of TONES 3 were higher compared to that in placebo patients, but we include this via the cost of hospitalisation, which increases the company's base-case ICER (with ERG corrections) by a relatively small amount (£1,000, see our response to the next query below).
P92, Table 29, HRG Codes	Amend column 3 header to: "National	National average unit costs, as sourced from NHS Reference costs refers to the average cost per finished consultant episode *and not the cost per day*. As such the average length of stay is not relevant, and if applied to	Thank you for bringing this to our attention. Table 29 has now been updated and the modelled hospitalisation cost corrected. All analyses using hospitalisation costs have

Table 29, Column 3 label "National average unit cost **(per day)**"	average unit cost" Delete: Column 4 "Average length of stay". Any further places where this data is used should also be corrected (e.g. Table 34, p102, row 15 "The cost of hospitalisation due to AEs", ERG analysis) and the economic analyses using this data should re-run.	the unit cost, as seems to be the case for the ERG analyses, would produce a substantial overestimate of the per episode hospitalisation cost.	been re-run. Amending the hospitalisation cost (per episode) increased the company's base-case ICER (with ERG corrections) by approximately £1,000. The updated ERG base case is £[redacted] per QALY gained.
P92, ERG conclusion on costs, Paragraph 1 under Table 29 "The company may have underestimated the cost of doctor	The company would like the ERG to amend this statement in line with our justification provided.	As outlined on CS p170, Paragraphs 2–4, the cost of additional consultations associated with titration/response assessment were included for solriamfetol treatment. The 37.5/75 mg doses were associated with 1 additional consultation, and the 150mg dose was associated with 2 additional consultations.	The conclusion has been amended as follows: "TONES 5 CSR states that "[redacted]." Since the company include the costs of only one and two consultations in the solriamfetol 75 mg and 150 mg arms, respectively, the cost

appointments for consultations on solriamfetol dose increases, as the model does not include an additional cost of one consultation in these arms.“			of doctor appointments for consultations on solriamfetol dose titration may have been underestimated.“ Note, however, that we did not make any corrections to this assumption since the effect on the ICER of making such corrections is relatively small.

Issue 27 ERG cumulative analysis and base case results

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
P108, Table 38 Row title “Sol dose split: 25%:50%:25%”	Amend to: “Sol dose split: [redacted]	CiC markup is missing from this row title	CiC added. Similarly, in Tables 36 and 37.

Issue 28 Appendices

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
P114, S9.1, Paragraph 2 “are assumed to equal 46.8% of those observed “	Amend to: “are assumed to equal 56.8% of those observed “	Edit corrects a typographical error to the value provided.	We confirm that the proportion 46.8% is correct. No changes made
P115, Table 40, Hospitalisation due to serious AEs	The company seeks additional clarification about this table, in combination with Issue 26	See Issue 26.	See our response to Issue 27.

Issue 29 Appendix 9.5, P119, Table Errors

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
P119, Appendix 9.5, Table, Row "Population characteristics"	Row: "Population characteristics" AiC mark-up has been added to relevant data points	There was AiC markup missing from these table rows in Appendix 9.5. The relevant AIC markup has been added in the table excerpt below.	Marking added, thank you.
P121 Appendix 9.5, Table, Row "Health state utilities"	Row "Health state utilities" AiC mark-up has been added to relevant data points		Marking added, thank you.

Issue	Company's analysis	ERG comments	ERG analysis
Decision problem			
Population characteristics	Base case: baseline demographic characteristics from the mITT population of TONES 3: - mean age: [redacted] years - female: [redacted]% Mean baseline ESS from the mITT population of TONES 3, excluding patients with ESS=10: [redacted] Scenarios: ESS>12 at baseline	For model parameterisation, the company use the baseline demographic and disease characteristics of the mITT population of the pivotal TONES 3 trial, excluding patients with ESS=10 at baseline (CS Table 25), whereas in the European marketing authorisation for SOL (CS Appendix C), EDS is associated with the ESS score of at least 10 points. The company do not provide a rationale for exclusion of patients with baseline ESS=10 from their analysis. As stated in CS KOL Clinical Practice Interviews, the decision to start treatment may depend on other factors, such as driving status, and treatment can be initiated in patients whose driving is affected even if their EDS is low. Therefore, excluding patients with ESS=10 from the analysis may not be justifiable. Clinical advice to the ERG suggests that the average ESS score at baseline observed in the TONES 3 trial is higher than that in patients with residual EDS in clinical practice. In the ERG base case, we use baseline characteristics of the whole mITT population from TONES 3, i.e. patients with baseline ESS score of at least 10 points. We conduct SAs for the threshold of ESS>10 and ESS>12.	Base case: baseline demographic and disease characteristics from the whole mITT population of TONES 3, including patients with ESS=10 at baseline: - mean age: [redacted] years - female: [redacted]% - mean baseline ESS: [redacted] Scenarios: - the patient sub-population with ESS>10 at baseline (as in the company's base case) - the patient sub-population with ESS>12 at baseline
Health state utilities			
Patient utility for OSA with EDS	Base case: EQ-5D-5L utilities estimated as a function of ESS from de novo mapping with 2016-2017 EU5 NHWS data	EQ-5D-5L results from the TONES 3 trial are not used in the economic model. [redacted]. The company argue that this is because the EQ-5D is insensitive because of the high baseline values in the	Base case: no change Scenarios: no change

Issue	Company's analysis	ERG comments	ERG analysis
	Scenarios: - EQ-5D-3L utilities mapped from ESS (McDaid 2007) - TTO utility for health state descriptions with different levels of ESS severity from survey of general public	TONES 3 population. We acknowledge this point but note that the lack of evidence of effect from the EQ-5D-5L in TONES 3 does raise uncertainty over the effectiveness of SOL at improving utility in this population. The company base case model estimates utility as a function of ESS and other patient characteristics, based on a new mapping from NHWS data. NHWS coefficients are the most influential model parameters in the company base case. Two alternative sources of utility estimates are used in scenario analysis: the McDaid et al. mapping from the NICE appraisal of CPAP for OSA (TA139); and a new TTO study. The ERG agrees that the NHWS mapping is the best available source of utility estimates, and the McDaid formula is a suitable alternative. We do not favour use of the TTO estimates.	

Issue 30 Date of document

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
ERG report front page	Potential amendment of date of completion of ERG report	The report is currently dated as 8th February 2021. We are unclear if this is an error or reflects a future stage of the process.	This appears to be an error in our report. We stated "Originally submitted 23/07/20. This version submitted 08/02/21 following factual accuracy check and revised company submission." However, this appears to have been corrected in the copy of the report included in the NICE committee papers which states 08/02/21. We have corrected our version accordingly.

Issue 31 Model Population

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
ERG report Issue 2, Page 12, Row 3 "The company's base case ICER increases from £34,121 to £36,118 per QALY with the ESS ≥10 population. Increasing the baseline ESS threshold for the population to ESS>12 reduces the base case ICER to £29,024 per QALY."	"The company's base case ICER (with ERG corrections) increases from £34,121 to £36,118 per QALY with the ESS ≥10 population. Increasing the baseline ESS threshold for the population to ESS>12 reduces the base case ICER to £29,024 per QALY.	The values for the ERG ICERs although similar to the company base case, are slightly different. As such, we feel to avoid confusion, the report must specify where the results are the ICERs of the company base case/ERG corrections (as opposed to the original CS company base case).	Amended

Issue 32 Definition of treatment response

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
ERG report Issue 4, Page 13, Row 3 "With a response definition of an ESS reduction of 2 or more points, there is a small increase in the company's base case ICER . A definition of 4 or more points reduces the company's base case ICER to £32,500 per QALY"	"With a response definition of an ESS reduction of 2 or more points, there is a small increase in the company's base case ICER (with ERG corrections). A definition of 4 or more points reduces the company's base case ICER to £32,500 per QALY"	The values for the ERG ICERs although similar to the company base case, are slightly different. As such, we feel to avoid confusion, the report must specify where the results are the ICERs of the company base case/ERG corrections (as opposed to the original CS company base case).	Amended

Issue 33 Background information on solriamfetol

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Section 2.2.2, Last Paragraph, p22 "Solriamfetol is orally administered once daily, and is available in doses of 37.5 mg, 75	"Solriamfetol is orally administered once daily, and is available in doses of 37.5 mg, 75 mg, and 150 mg. The recommended starting dose is 37.5 mg for patients with OSA which can be	As agreed in Issue 6 of the previous factual accuracy check responses, this statement should reflect the SmPC posology for the indication under review (the	Amended

mg, and 150 mg. The recommended starting dose is 37.5 mg which can be titrated at intervals of at least three days up to a maximum dose of 150 mg"	titrated at intervals of at least three days up to a maximum dose of 150 mg	starting dose differs for the indication in narcolepsy assessed in ID1602)	

Issue 34 Section 4.1, ERG comment on company's review of cost-effectiveness evidence

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Section 4.1, p63, first paragraph "An overview of the key assumptions of the economic analyses submitted for TA130 is presented in CS Table 24"	"An overview of the key assumptions of the economic analyses submitted for TA139 is presented in CS Table 24"	There is a minor typo in the name of the relevant NICE TA (139 for CPAP in OSA).	Corrected

NICE National Institute for Health and Care Excellence

Technical engagement response form

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

As a stakeholder you have been invited to comment on the ERG report for this appraisal. The ERG 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 key issues below. You do not have to provide a response to every issue. 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 included in the committee papers in full and may also be summarised and presented in slides at the appraisal committee meeting.

Deadline for comments 5pm on Friday 5 February 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 ERG report which summarises the background and submitted evidence, and presents the ERG's summary of key issues, critique of the evidence and exploratory analyses. This will provide context and describe the questions below in greater detail.
- Please ensure your response clearly identifies the issue numbers that have been used in the executive summary of the ERG report. If you would like to comment on issues in the ERG report that have not been identified as key issues, you can do so in the 'Additional issues' section.
- If you are the company involved in this appraisal, please complete the 'Summary of changes to the company's cost-effectiveness estimates(s)' section if your response includes changes to your cost-effectiveness evidence.
- 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 Pharmaceuticals**
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	

Key issues for engagement

Please use the table below to respond to questions raised in the ERG report on key issues. You may also provide additional comments on the key issue that you would like to raise but which do not address the specific questions.

Key issue	New evidence, data or analyses?	Response
What additional evidence or analyses might help to resolve this key issue?		
Jazz acknowledge that the ERG issues included the definition of ESS response, compliance to primary OSA therapy, the natural change in ESS over time, and the definition of normal sleepiness (EDS). Jazz have conducted additional interviews with 10 KOLs to gain further advice on these topics (see separate file: CONFIDENTIAL. Post ERG Report KOL Interviews (1)).		
Key issue 1: Potential reduction in patient compliance with primary OSA therapy during concomitant solriamfetol treatment [report section 3.2.6.1.4]	YES	In the CS, an exploratory analysis of compliance with primary OSA therapy was presented. We recognise this as an important factor that clinicians will consider in treating patients, particularly if the addition of pharmacotherapy were to compromise compliance with primary OSA therapy. A peer-reviewed manuscript has since been published comprehensively answering this important issue (2). Herein, the authors conclude solriamfetol treatment did not impact primary OSA therapy compliance and that this is consistent with other wake-promoting agents studied in this context. Moreover, the study concluded that the magnitude of the wake-promoting effects of solriamfetol treatment for up to 1 year is similar regardless of compliance to primary OSA therapy. This study included 417 participants with diagnosed OSA exposed to solriamfetol and using primary therapy for OSA (i.e. continuous positive airway pressure, oral pressure therapy, oral appliance, or upper airway stimulator, history of attempting primary OSA therapy use, or history of surgical intervention to treat OSA). The population is drawn from registered trials (NCT02806895/Eudra CT 2015-003930-28 and NCT02806908/Eudra CT 2015-003931-36) and trials with previously published results (3-7) and the

Key issue	New evidence, data or analyses?	Response
What additional evidence or analyses might help to resolve this key issue?		
		analysis set used was the safety population within those studies. The inclusion of participants with varying levels of compliance to primary OSA therapy provided a study population representative of patients in real-world clinical practice. The methodology of this study is fully declared, and the impact of the missing primary OSA therapy fully discussed by the authors. Missing data were handled using a last observation carried forward approach. The study concluded that "the number of participants who remained in the study but did not report primary OSA therapy use data was not substantial". UK KOLs advise that a reduction in compliance with CPAP is not expected, as solriamfetol would not be offered as an alternative to primary therapy (1). They state that some patients might stop CPAP if they believe they can use pharmacotherapy as alternative, if not properly educated. They state that this could be mitigated with education as to the benefits and requirement for CPAP, as a reiteration of the education provided when a patient is initiated onto CPAP.
Key issue 2: Model population [report section 4.2.3]	NO	The demographics and baseline disease characteristics of the CS model cohort were based on the patient population of TONES 3, however for the reasons outlined below, patients with a baseline ESS=10 were excluded. Upon review of the ERG's comments, however, Jazz investigated this topic in detail. Jazz has now established that patients with ESS scores > 12 would have the greatest clinical need and derive the most benefit from solriamfetol. This is evidenced by the improvement in QoL demonstrated in the NHWS Survey (Appendix N of the CS (8)) in which data indicated minimal improvement in QoL at ESS levels <12, with more substantial improvement in QoL demonstrated at ESS scores >12. In addition, there is evidence to show that the socioeconomic burden of ESS 11–12 is very similar to that of no EDS (9).

		[redacted] (10). Jazz recognise that clinicians use ESS as part of a holistic assessment of a patient's EDS symptoms. ESS scores ≤10 are considered within the normal range in the UK, for example the NICE Clinical Knowledge Summary for Obstructive Sleep Apnoea Syndrome (11) references the ESS questionnaire as an assessment method and states 'a total [ESS] score greater than 10 indicates abnormal daytime sleepiness' (11-13). This is further supported by other publications in which ESS was demonstrated as a validated measure with high specificity and sensitivity for assessing patient-reported subjective sleepiness (12, 13), and in UK KOL feedback from pre-submission and post-ERG report Clinical Practice Interviews in which only one clinician viewed an ESS of 10 as abnormal (14). Given that in the UK, ESS scores ≤10 are considered 'normal' daytime sleepiness, in clinical practice, patients with OSA may have ESS scores substantially in excess of 10 at treatment initiation. However, our original company model included only those patients with ESS > 10 in order to align to the NICE Clinical Knowledge Summary, published literature, and expert opinion in the UK. Furthermore, although ESS scores ≤10 are within the normal range, defining a response as 'normalised' or ESS ≤10 would not reflect clinical practice. Based on UK KOL feedback from pre-submission and post-ERG report Clinical Practice Interviews, EDS is multidimensional and what is considered 'normal' is highly specific to the individual patient; KOLs advise that the patient's self-reported improvement in condition, and/or a reduction of 2–4 points in ESS reflects a clinically meaningful response to treatment (1, 14). Based on this KOL evidence, instead of using 'normalised' to define a response to treatment in the model, the midpoint value of ≥3 point reduction in ESS was used to define a response in the base case analysis, with scores of ≥2 and ≥4 assessed in scenario analyses. The solriamfetol EPAR (15) states that the entry requirement into the TONES studies required that patients had ESS ≥ 10, rather than description in the ERG report, which states 'the definition of EDS from the European Medicines Agency… [is] ESS ≥ 10'. The EPAR reflects the eligibility criteria for the TONES studies and not the definition of normalisation of a patient in UK clinical practice.

Key issue	New evidence, data or analyses?	Response
What additional evidence or analyses might help to resolve this key issue?		
		In summary, Jazz believe that the clinically appropriate patient population for solriamfetol is those patients with baseline ESS > 12 and we recognise that although the definition of 'normal' ESS is patient-specific, and highly individualised, the generally agreed definition in the UK is that normal ESS is > 10.
Key issue 3: Definition of treatment response [report section 4.2.6.3]	**NO**	Jazz agree that there is considerable variation in the definition of treatment response. However, UK clinical experts agree that ESS is a commonly used factor in decision making around disease severity and response to treatment with regards to EDS in patients with OSA. As a key part of the decision making process around the current disease state of a patient, it is put into context in individualising therapy, and optimising treatment. Patel et al., 2018 (16) describe the minimally important clinical difference (MICD) in a prospective study of patients being initiated on CPAP, that is, the smallest change in ESS that could be considered beneficial or detrimental with respect to sleepiness. They concluded that the MICD for ESS change was between −2.65 and −2.21, the range representing the use of both anchor- and distribution-based methods of estimation. As an ordinal scale, this corresponds to a change in a single patient of between 2 and 3 points to detect the minimum difference. Normalisation of ESS may occur with a greater or lesser magnitude change, depending on baseline severity. This would therefore only capture the MICD patients that improve from an ESS of 11 to 13. Applying this definition would be overly stringent and may bias against clinically important changes in patients' ESS when baseline measurements are 14 or greater, for whom a change may actually be more valuable given the increasing burden with increasing EDS. This scenario has therefore not been considered. Although the final goal of treatment may be normalisation of EDS, an improvement in ESS of between 2 and 3 would still represent a clinically significant improvement in EDS for a patient. UK KOL Evidence from both the pre-submission and post-ERG report Clinical Practice Interviews shows that clinicians may accept variable levels of ESS improvement, and/or any patient reported improvement in condition as meaningful (1, 14). In general, as long as the patient feels that treatment improves their

Key issue	New evidence, data or analyses?	Response
What additional evidence or analyses might help to resolve this key issue?		
		condition, daily function or usual activities, many clinicians will accept this to be a meaningful and effective response to treatment. In TONES 3, all solriamfetol arms (37.5, 75, 150 mg) achieved a ≥3 point reduction in mean ESS scores (-5.0, -5.1 and -7.7 point reduction, respectively) after 12 weeks of treatment (CS Section B.2.6.1). Furthermore, in TONES 5, both groups receiving solriamfetol achieved a ≥3 point reduction in mean ESS scores after 2 weeks, maintained for up to 52 weeks (CS Section B.2.6.2).
Key issue 4: Adjustment for the placebo effect ('centring') [report section 4.2.6.2]	YES	Key Issue 4 and Key Issue 7 are interlinked. The full response to both of these issues is provided below this table, in the Full company response to Key Issues 4 and 7.
Key issue 5: Health utility values [report section 4.2.7]	YES	Substantial consideration was given to understand which utility set would provide the most robust data set to describe the relationship between ESS and utility. A larger data set, or one which probed the specific impact of EDS on utility likely best reflects the impact of EDS on the patient. A discussion was provided in the CS about the reasons trial data may not fully reflect a UK population from a utility perspective including the high baseline values despite significant impairment, differences in driving regulations between the UK/EU and US and the length of time needed for a population to realise a new normal and adapt their behaviour. The cost effectiveness of the current treatment paradigm in OSA is based around the use of the McDaid algorithm, and therefore it was felt to be important to include a scenario using this utility score. However it

Key issue	New evidence, data or analyses?	Response
What additional evidence or analyses might help to resolve this key issue?		
		is also felt that the larger sample size from the NHWS study provided an opportunity to understand the most appropriate shape for relationship between ESS and EQ-5D. In the original NHWS utility mapping study, the country-specific utility value for each patient was used. Therefore these values have been mapped across to the UK value set in the amended (Appendix N of the CS (8)). It can also be confirmed that the NHWS mapping study was completed in line with NICE DSU guidelines. These values have been updated in the company's cost effectiveness model. Finally, estimates derived from the generic measure should be considered to be conservative, as the likely slope is steeper as suggested by the Time Trade Off (TTO) methodology (ICER £[redacted]).
Key issue 6: Partner utilities [report section 4.2.7.4]	NO	The NICE reference case states that economic evaluations should include 'all direct health effects, whether for patients or, when relevant, carers', with section 5.1.7 stating 'the perspective on outcomes should be all direct health effects, whether for patients or other people. The perspective adopted on costs should be that of the NHS and personal and social services.' With that in mind, Jazz looked to quantify the health effects of improvement in EDS beyond those attributed directly to the patient. Due to a combination of factors including the impact of EDS on the patient-partner/carer relationship, the family dynamic, ability to help with day-to-day life and for partners to be able to enjoy a social life with their partner, and potentially in their own right, the impact on marital relationships and the additional financial strain brought about by rEDS to the whole family, there is a substantial disutility to the partner of a patient with EDS due to OSA which is not typically considered when assessing the impact of treatment in clinical practice. Although it has not been possible to test the relationship in EQ-5D of a partner related to a patient's ESS, it is hypothesised that several of the domains of EQ-5D have the potential to be impacted, for example anxiety/depression and usual activities, which would be negatively impacted for a partner/carer resulting in

Key issue	New evidence, data or analyses?	Response
What additional evidence or analyses might help to resolve this key issue?		
		a decrease in HRQoL for the partner/carer. The Time Trade Off methodology allowed the relationship of partner utility and patient utility to be predicted and, therefore, this relationship is used as a scenario in the company submission to show that it is likely the true impact of solriamfetol on the HRQoL of patients and partners is likely to be higher than that presented in the base case for just patients alone. Jazz accepts the ERG statement that not all people with OSA will have partners as carers although a number of patients with rEDS in OSA may have their partners as a carer. This aside, it is believed that solriamfetol will have an effect on HRQoL beyond the patients treated and Jazz has presented this as a scenario (i.e. not included in the base case) which suggests the true ICER could be lower than the base case. Note that the utility gain was only applied to the proportion of TONES 3 participants who were married (66%). Including the partner utilities reduces the ICERs in all three HRQoL datasets (NHWS, Mc Daid and TTO). Jazz welcomes clarification from the Committee regarding whether or not partner utilities should be included as a health effect for solriamfetol.
Key issue 7: Treatment discontinuation and loss of response rates [report section 4.2.6.4]	YES	Key Issue 4 and Key Issue 7 are interlinked. The full response to both of these issues is provided below this table, in the Full company response to Key Issues 4 and 7.

<table>
<tr><th>Key issue</th><th>New evidence, data or analyses?</th><th>Response</th></tr>
<tr><td colspan="3">What additional evidence or analyses might help to resolve this key issue?</td></tr>
<tr><td>Key issue 8: The impact of adverse events [report section 4.2.8.3.2]</td><td>YES</td><td>We agree with the ERG position that trial data with respect to adverse event management would not necessarily apply to English clinical practice. (4.2.8.3 Resource use Health state unit costs and resource use are discussed in CS sections B.3.5.1.2 and B.3.5.2.). We therefore conducted an analysis in the English Hospital Episodes Statistics, which describes the current management of the reported AEs (Table 40 Hospitalisation due to serious AEs in ERG report).

The population was selected using the following criteria to closely match study TONES 5:

<table>
<tr><td>Sleep Apnoea Patients - any diagnosis - Jun 2015 - Nov 2017 - IP and OP</td><td>[redacted]</td></tr>
<tr><td>Exclusion criteria</td><td></td></tr>
<tr><td>Pregnancy during index period or up to 12 months before</td><td>[redacted]</td></tr>
<tr><td>Age under 18 years</td><td>[redacted]</td></tr>
<tr><td>ICD10 of F* anytime prior to or during index period</td><td>[redacted]</td></tr>
<tr><td>Cardiac HRG anytime prior to or during index period</td><td>[redacted]</td></tr>
<tr><td>Bariatric surgery anytime prior to or during index period</td><td>[redacted]</td></tr>
<tr><td>Diagnosis of CKD anytime prior to or during index period</td><td>[redacted]</td></tr>
<tr><td>Total patients who meet the inclusion/exclusion criteria (N)</td><td>[redacted]</td></tr>
</table>
</td></tr>
</table>

In this population, the presentation of the specified AEs (Table 40 ERG report), resulted in the following rate of presentation and admission to secondary care services:

Metrics for April 2018 and March 2020	Total Patients	% of N	Average LOS
Ear and labyrinth disorders/ Vertigo/Vertigo	[redacted]	[redacted]	[redacted]
Gastrointestinal disorders/ Abdominal pain/ ABDOMINAL PAIN	[redacted]	[redacted]	[redacted]
Gastrointestinal disorders/ Nausea/ NAUSEA INTRACTABLE	[redacted]	[redacted]	[redacted]
General disorders and administration site conditions/ Chest pain/ Chest pain /Unknown	[redacted]	[redacted]	[redacted]
Infections and infestations/ Bronchitis/ ACUTE BRONCHITIS	[redacted]	[redacted]	[redacted]
Injury, poisoning and procedural complications/ Alcohol poisoning/ acute alcohol intoxication	[redacted]	[redacted]	[redacted]
Injury, poisoning and procedural complications/ Ear canal injury/ laceration of right ear canal	[redacted]	[redacted]	[redacted]
Injury, poisoning and procedural complications/ Head injury/ blunt head injury	[redacted]	[redacted]	[redacted]
Injury, poisoning and procedural complications/ Skull fracture/ closed fracture of parietal bone of skull	[redacted]	[redacted]	[redacted]
Injury, poisoning and procedural complications/ Skull fractured base/ closed fracture of temporal bone	[redacted]	[redacted]	[redacted]
Nervous system disorders/ Cerebrovascular accident/ Stroke	[redacted]	[redacted]	[redacted]

Key issue	New evidence, data or analyses?	Response
What additional evidence or analyses might help to resolve this key issue?		
		Of particular note, “Nervous system disorders/ Cerebrovascular accident/ Stroke” occurred in 2.75% (“common” by WHO definition) of the real-world population in the absence of exposure to solriamfetol. By contrast, in the open label extension study TONES 5 population (which had no comparator arm) stroke was rare (only a single patient, <1%). This indicates the inclusion of stroke in the ERG model would be an undue cost associated with solriamfetol, as stroke already occurs in the target population in the existing clinical landscape without solriamfetol. The addition of stroke by the ERG is a major cost driver, and should not be attributed to solriamfetol when stroke already occurs as a population risk. As TONES 5 trial patients were monitored in a more intense way than in clinical practice where clinicians suggest that follow up is usually at 3-6 monthly intervals (with planned [redacted] by phone throughout the study) (17), there was potentially a lower threshold to admit to hospital in the context of the TONES 5 population. In contrast, in the HES population, presence of the list of AEs (Table 40 in ERG Report) in a real-world population rarely resulted in admission (e.g. vertigo in 0.25% of patients) and often resulted in short average length of stays of 1-2 days when they occurred. This suggests that many adverse events would be managed in a community setting they occurred in English clinical practice and is consistent with the KOL Clinical Practice interviews (14).

Key issue 9: Solriamfetol dose split [report section 4.2.8.1.2]	YES	Due to the absence of any other pharmacotherapies licensed and indicated for the management of EDS due to OSA, UK clinicians were unable to describe what the final dose split of solriamfetol 37.5, 75 and 150 mg may be in practice. However, based on feedback from KOLs experienced in the use of wake promoting agents for the management of EDS due to narcolepsy, it is anticipated that clinicians in the UK will titrate solriamfetol slowly starting at the lowest dose (37.5 mg) (14). Early data from one US source suggest a [redacted] dose split for the 37.5, 75 and 150 mg doses of solriamfetol, respectively, but it is anticipated that UK prescribers will be more conservative than those of the US, and that in UK clinical practice, solriamfetol will have a 40/40/20 dose split. This may be considered a conservative approach given that in TONES 3 approximately 52% of patients on 37.5 mg dose achieved normal ESS scores (ESS ≤ 10) by week 12 (18), thus in clinical practice would not titrate to a higher dose. Due to the randomised nature of TONES 3, the dose split from the clinical trial programme for solriamfetol in OSA is unlikely to be fully reflective of the dose split that may be observed in clinical practice, where if a patient normalises on a particular dose, it is expected that the patient will remain on that dose (and would not titrate unnecessarily to a higher dose). UK Clinicians report that the dose split would be determined by response rate, and that prescribers aim for the lowest effective dose (14). In the TONES 3 trial approximately 52% of patients normalised with respect to ESS on 37.5 mg (18). As normalisation of ESS is a stringent measure of efficacy, and recognised by UK clinicians, the combination of the TONES 3 observed efficacy, and the expected principles of prescribing by UK clinicians, it could be reasonably expected that ~40% patients would remain on the 37.5 mg dose, as per the CS base case analysis. We have found no evidence to support the ERG's assumption that the dose split could be 20/40/40. UK clinicians experienced in the management of narcolepsy (14) describe taking a cautious approach to titration, often with longer intervals than occurred in the trial, with a dose increment interval of weeks, to months. Subjective descriptions of attitudes to prescribing by UK KOLs includes "start low" and "slow titration" for other pharmacotherapies used in sleep medicine and it would be reasonable to expect a

Key issue	New evidence, data or analyses?	Response
What additional evidence or analyses might help to resolve this key issue?		
		similar approach for an indication with no current licensed therapies. This creates an expectation that lower doses when demonstrated to be effective and well-tolerated would be maintained. This informs the 40:40:20 dose split that is the base case model.

Additional issues

Jazz have no additional issues to include.

Summary of changes to the company's cost-effectiveness estimate(s)

Changes to the original assumptions in the CE model when using the solriamfetol LIST price are presented below:

Key issue(s) in the ERG report that the change relates to	Company's base case before technical engagement	Change(s) made in response to technical engagement	Impact on the company's base-case ICER
		Company's original base-case ICER (list price):	£34,106
Key issue 2: Model population [report section 4.2.3]	The company's original preferred assumption was that solriamfetol would be available to patients with EDS due to OSA at an ESS score >10	The company's new base case considers only those patients with an ESS >12	Revised ICER: £29,014 Δ Incremental cost: £878 Δ Incremental QALY: 0.068 Δ ICER: -£5,092
Key issue 5: Health utility values [report section 4.2.7]	In the original company model, the NHWS utility mapping algorithm was based on an outdated version of the study in which the country specific utility value for each patient was used.	The company's new base case considers values have been mapped across to the UK value set in the amended report in line with the NICE DSU.	Revised ICER: £31,657 Δ Incremental cost: £0 Δ Incremental QALY: 0.017 Δ ICER: -£2,449
Key issue 7: Treatment discontinuation and loss of response rates [report section 4.2.6.4]	The company's original preferred assumption was that discontinuation rates were not applicable to the standard of care without solriamfetol arm.	The company's new base case considers the values for discontinuation as outlined by the ERG.	Revised ICER: £35,338 Δ Incremental cost: £2,390 Δ Incremental QALY: 0.060 Δ ICER: £1,233
Company's updated preferred base case following technical engagement (using the solriamfetol list price)	Incremental QALYs: 0.166	Incremental costs: £3,487	Revised ICER: £28,453 Δ Incremental cost: £3,487 Δ Incremental QALY: 0.166 Δ ICER: -£5,652

Changes to the original assumptions in the CE model when using the solriamfetol PAS price are presented below:

Key issue(s) in the ERG report that the change relates to	Company's base case before technical engagement	Change(s) made in response to technical engagement	Impact on the company's base-case ICER
		Company's original base-case ICER (list price):	£[redacted]
Key issue 2: Model population [report section 4.2.3]	The company's original assumption was that solriamfetol would be available to patients with EDS due to OSA at an ESS score >10	The company's new base case considers only those patients with an ESS >12	Revised ICER: £[redacted] Δ Incremental cost: £[redacted] Δ Incremental QALY: 0.068 Δ ICER: [redacted]
Key issue 5: Health utility values [report section 4.2.7]	In the original company model, the NHWS utility mapping algorithm was based on an outdated version of the study in which the country specific utility value for each patient was used.	The company's new base case considers the NHWS values mapped to the UK value set in the amended report in line with the NICE DSU.	Revised ICER: [redacted] Δ Incremental cost: [redacted] Δ Incremental QALY: 0.017 Δ ICER: [redacted]
Key issue 7: Treatment discontinuation and loss of response rates [report section 4.2.6.4]	The company's original assumption was that discontinuation rates were not applicable to the standard of care without solriamfetol arm.	The company's new base case considers the values for discontinuation in the standard of care without solriamfetol arm as outlined by the ERG.	Revised ICER: [redacted] Δ Incremental cost: [redacted] Δ Incremental QALY: 0.060 Δ ICER: [redacted]
Company's preferred base case following technical engagement	Incremental QALYs: 0.166	Incremental costs: [redacted]	Revised ICER: [redacted] Δ Incremental cost: [redacted] Δ Incremental QALY: 0.166 Δ ICER: [redacted]

Full cost effectiveness analysis at PAS price and updated model assumptions (Company's preferred base case following technical engagement)

The following tables provide detailed supporting analyses for the revised company base case result (using solriamfetol PAS price). Results include:

- Base case analysis
- Sensitivity analysis
- Threshold analysis
- Scenario analysis
- Subgroup analysis

The key assumptions are as listed below:

New assumptions	Unchanged assumptions
o PAS price of [redacted] per 75 mg table and [redacted] per 150 mg tablet o A revised form of the NHWS mapping algorithm which now utilizes the UK weighting scores o The ERGs preferred estimates of discontinuation due to loss of efficacy and adverse events for solriamfetol – Note that with the centred IPD data discontinuation in the standard of care arm is not applicable. o Baseline ESS score of >12	o Centred IPD data (Adjusting both solriamfetol and placebo/standard of care arms for the Hawthorne effect so that only the incremental benefit of solriamfetol is considered) o A 40/40/20 dose split between 37.5 mg/75 mg/150 mg (i.e. the ratio of doses of solriamfetol anticipated in UK practice across all patients on a stable, post-titration dose) o Response equal to a reduction in ESS of 3 or more

A full summary of specific variables applied is provided in the table below.

Summary of variables applied in the economic model

Variable	Value	Measurement of uncertainty and distribution: CI (distribution)
Discount rate: Costs	3.5%	0.0% - 6.0% (Not varied)
Discount rate: Outcomes	3.5%	0.0% - 6.0% (Not varied)
Average age at baseline	[redacted]	[redacted]
Proportion of cohort that are female	[redacted]	[redacted]
Solriamfetol - 75 mg: Pack size	28.0	28.0 - 28.0 (Not varied)
Solriamfetol - 150 mg: Pack size	28.0	28.0 - 28.0 (Not varied)
Solriamfetol - 75 mg: Pack price	[redacted]	[redacted]
Solriamfetol - 150 mg: Pack price	[redacted]	[redacted]
ESS => EQ-5D: McDaid - Constant	0.893	0.836 - 0.949 (Normal)
ESS => EQ-5D: McDaid - ESS	-0.010	-0.018 - -0.002 (Normal)

Variable	Value	Measurement of uncertainty and distribution: CI (distribution)
ESS => EQ-5D: McDaid - Baseline ESS	0.003	-0.004 - -0.010 (Normal)
Discontinuation - LoE (Year 1): solriamfetol 150 mg	[redacted]	[redacted]
Discontinuation - LoE (Year 1): solriamfetol 75 mg	[redacted]	[redacted]
Discontinuation - LoE (Year 1): solriamfetol 37.5 mg	[redacted]	[redacted]
Discontinuation - LoE (Year n): solriamfetol 150 mg	[redacted]	[redacted]
Discontinuation - LoE (Year n): solriamfetol 75 mg	[redacted]	[redacted]
Discontinuation - LoE (Year n): solriamfetol 37.5 mg	[redacted]	[redacted]
Discontinuation - TEAEs (Year 1): solriamfetol 150 mg	[redacted]	[redacted]
Discontinuation - TEAEs (Year 1): solriamfetol 75 mg	[redacted]	[redacted]
Discontinuation - TEAEs (Year 1): solriamfetol 37.5 mg	[redacted]	[redacted]
Discontinuation - TEAEs (Year n): solriamfetol 150 mg	[redacted]	[redacted]
Discontinuation - TEAEs (Year n): solriamfetol 75 mg	[redacted]	[redacted]
Discontinuation - TEAEs (Year n): solriamfetol 37.5 mg	[redacted]	[redacted]
Cost of discontinuation - TEAEs	£37	£30 - £44 (Gamma)
NHWS mapping - Constant coefficient	[redacted]	[redacted]
NHWS mapping - ESS Score: 0-11 coefficient	[redacted]	[redacted]
NHWS mapping - ESS Score: 12-14 coefficient	[redacted]	[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]
NHWS mapping - Female coefficient	[redacted]	[redacted]
NHWS mapping - Married coefficient	[redacted]	[redacted]
NHWS mapping - Medium Income coefficient	[redacted]	[redacted]

Variable	Value	Measurement of uncertainty and distribution: CI (distribution)
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]
Proportion of patients receiving solriamfetol 37.5 mg	40%	20% - 60% (Dirichlet)
Proportion of patients receiving solriamfetol 75 mg	40%	20% - 60% (Dirichlet)
Proportion of patients receiving solriamfetol 150 mg	20%	0% - 40% (Dirichlet)

Abbreviations: BMI, body mass index; CCIQuan, Charlson Comorbidity Index; 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.

Base-case results

Base-case results – weighted ICER

Technologies	Total costs (£)	Total QALYs	Total LYG	Incremental costs (£)	Incremental QALYs	ICER versus baseline (£/QALY)
Standard of care without solriamfetol	£0	11.524	30.213			
Standard of care with the addition of solriamfetol (40/40/20 37.5, 75, 150 mg)	[redacted]	11.906	30.213	[redacted]	0.383	[redacted]

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

Base-case results using the bootstrapping method – weighted ICER

Technologies	Total costs (£)	Total QALYs	Total LYG	Incremental costs (£)	Incremental QALYs	ICER versus baseline (£/QALY)
Standard of care without solriamfetol	£0	11.478	30.034			
Standard of care with the addition of solriamfetol (40/40/20 37.5, 75, 150 mg)	[redacted]	11.858	30.034	[redacted]	0.381	[redacted]

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

Sensitivity analyses

Probabilistic sensitivity analysis

The probability that solriamfetol would be the most cost-effective treatment at a threshold of £20,000 per QALY was [redacted]%, and at a threshold of £30,000 per QALY, this increased to [redacted]%. Across 5,000 PSA simulations, solriamfetol was associated with a mean cost of £[redacted] (95% CI: £[redacted]) and mean total QALYs of 12.236 (95% CI: 12.225, 12.247). These results are highly congruent with the deterministic results. Overall, the results remain consistent with the base case analysis.

Cost-effectiveness acceptability curve

[redacted]

Abbreviations: SoC, standard of care.

Probabilistic sensitivity analysis results

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER incremental (£/QALY)
Standard of care without solriamfetol	£0 (£0 - £0)	11.868 (11.857 - 11.879)			
Standard of care with the addition of solriamfetol (40/40/20 37.5, 75, 150 mg)	[redacted]	12.236 (12.225 - 12.247)	[redacted]	0.368	[redacted]

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

Deterministic sensitivity analysis

Univariate analysis: standard of care with the addition of solriamfetol versus standard of care without solriamfetol

[redacted]

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

Univariate analysis: standard of care with the addition of solriamfetol versus standard of care without solriamfetol

Variable (lower bound to upper bound; base case value)	ICER with lower bound	ICER with upper bound
Discount rate: Costs (0.0% to 6.0%; base case 3.5%)	[redacted]	[redacted]
NHWS mapping - ESS Score: 12-24 coeff [redacted]	[redacted]	[redacted]
Discount rate: Outcomes (0.0% to 6.0%; base case 3.5%)	[redacted]	[redacted]
Proportion of patients on Sol 37.5 mg (20.0% to 60.0%; base case 40.0%)	[redacted]	[redacted]
Proportion of patients on Sol 75 mg (20.0% to 60.0%; base case 40.0%)	[redacted]	[redacted]
NHWS mapping - ESS Score: 0-11 coeff [redacted]	[redacted]	[redacted]
Discontinuation - LoE (Yr n): Sol 37.5 mg [redacted]	[redacted]	[redacted]
Discontinuation - TEAEs (Yr n): Sol 150 mg [redacted]	[redacted]	[redacted]
Average age at baseline (42.4 to 64.9; base case 53.7)	[redacted]	[redacted]
No. of HCP contacts during titration - 37.5mg (0 to 3; base case 1)	[redacted]	[redacted]

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

Threshold analysis

Threshold analysis: Results of threshold analysis: **standard of care with the addition of solriamfetol versus standard of care without solriamfetol**

Variable	Base case	Value to achieve ICER of:	
	(Lower bound – Upper bound)	£20,000 per QALY	£30,000 per QALY
Discount rate: Costs	3.5% (0.0% to 6.0%)	3.6%	-0.1%
NHWS mapping - ESS Score: 12-24 coeff	[redacted]	[redacted]	[redacted]

Discount rate: Outcomes	3.5% (0.0% to 6.0%)	3.4%	8.5%
Proportion of patients on Sol 37.5 mg	40.0% (20.0% to 60.0%)	41.0%	-58.3%
Proportion of patients on Sol 75 mg	40.0% (20.0% to 60.0%)	41.5%	-124.3%
NHWS mapping - ESS Score: 0-11 coeff	[redacted]	[redacted]	[redacted]
Discontinuation - LoE (Yr n): Sol 37.5 mg	[redacted]	[redacted]	[redacted]
Discontinuation - TEAEs (Yr n): Sol 150 mg	[redacted]	[redacted]	[redacted]
Average age at baseline	53.7 (42.4 to 64.9)	NA	NA
No. of HCP contacts during titration - 37.5mg	1 (0 to 3)	-13	689

Abbreviations: coeff, coefficient; ESS, Epworth Sleepiness Scale; ICER, incremental cost effectiveness ratio; LoE, loss of efficacy; NHWS, National Health and Wellness Survey; QALY, quality adjusted life year; TEAE, treatment emergent adverse events; Yr 1, Year one; Yr n, Years 2 and beyond.
* Outside credible range.
† Because the other doses are varied independently these scenarios are implausible (as the total share will exceed 100%).

Scenario analysis

Alternative model time horizon

Scenario analysis: Alternative model time horizon

Time horizon	Solriamfetol			
	37.5 mg	75 mg	150 mg	Weighted
5	[redacted]	[redacted]	[redacted]	[redacted]
10	[redacted]	[redacted]	[redacted]	[redacted]
15	[redacted]	[redacted]	[redacted]	[redacted]
20	[redacted]	[redacted]	[redacted]	[redacted]
25	[redacted]	[redacted]	[redacted]	[redacted]
30	[redacted]	[redacted]	[redacted]	[redacted]
35	[redacted]	[redacted]	[redacted]	[redacted]
40	[redacted]	[redacted]	[redacted]	[redacted]
45	[redacted]	[redacted]	[redacted]	[redacted]

Time horizon	Solriamfetol			
	37.5 mg	75 mg	150 mg	Weighted
50	[redacted]	[redacted]	[redacted]	[redacted]

Alternative definition of response

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

Technologies	Total costs (£)	Total QALYs	LYG	Incremental costs (£)	Incremental QALYs	Incremental ICER
Standard of care without solriamfetol	£0	11.524	30.213			
Standard of care with the addition of solriamfetol	[redacted]	11.936	30.213	[redacted]	0.412	[redacted]

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

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

Technologies	Total costs (£)	Total QALYs	LYG	Incremental costs (£)	Incremental QALYs	Incremental ICER
Standard of care without solriamfetol	£0	11.524	30.213			
Standard of care with the addition of solriamfetol	[redacted]	11.851	30.213	[redacted]	0.327	[redacted]

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

True placebo response for standard of care without solriamfetol

Scenario analysis: True placebo response for standard of care without solriamfetol

Technologies	Total costs (£)	Total QALYs	LYG	Incremental costs (£)	Incremental QALYs	Incremental ICER
Standard of care without solriamfetol	£0	11.524	30.213			

Technologies	Total costs (£)	Total QALYs	LYG	Incremental costs (£)	Incremental QALYs	Incremental ICER
Standard of care with the addition of solriamfetol	[redacted]	12.157	30.213	[redacted]	0.633	[redacted]

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

Disaggregated results utilising bootstrapping methods

Scenario analysis: **Results of the bootstrapping analysis on the raw mIPD – dose split 40/40/20**

Technologies	Total costs (£)	Total QALYs	Total LYG	Incremental costs versus baseline (£)	Incremental QALYs versus baseline	ICER versus baseline (£/QALY)
Standard of care without solriamfetol	£0 (£0 - £0)	11.478 (11.467 - 11.488)	30.034 (29.991 - 30.077)			
Standard of care with solriamfetol 37.5 mg	[redacted]	11.740 (11.730 - 11.751)	30.034 (29.991 - 30.077)	[redacted]	0.263	[redacted]
Standard of care with solriamfetol 75 mg	[redacted]	11.831 (11.820 - 11.842)	30.034 (29.991 - 30.077)	[redacted]	0.091	[redacted]
Standard of care with solriamfetol 150 mg	[redacted]	12.150 (12.138 - 12.161)	30.034 (29.991 - 30.077)	[redacted]	0.319	[redacted]

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

Alternative solriamfetol dose split

Scenario analysis: Disaggregated solriamfetol results by solriamfetol dose

Technologies	Total costs (£)	Total QALYs	Total LYG	Incremental costs versus baseline (£)	Incremental QALY versus baseline	ICER versus baseline (£/QALY)
Standard of care without solriamfetol	£0	11.524	30.213			
Standard of care with solriamfetol 37.5 mg	[redacted]	11.786	30.213	[redacted]	0.262	[redacted]
Standard of care with solriamfetol 75 mg	[redacted]	11.882	30.213	[redacted]	0.358	[redacted]
Standard of care with solriamfetol 150 mg	[redacted]	12.196	30.213	[redacted]	0.672	[redacted]

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

Scenario analysis: Alternative solriamfetol dose split: 37.5 mg -33%, 75 mg-33%, 150 mg-33%

Technologies	Total costs (£)	Total QALYs	LYG	Incremental costs (£)	Incremental QALYs	Incremental ICER
Standard of care without solriamfetol	£0	11.524	30.213			
Standard of care with the addition of solriamfetol	[redacted]	11.955	30.213	[redacted]	0.431	[redacted]

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

Scenario analysis: Alternative solriamfetol dose split: 37.5 mg -25%, 75 mg-50%, 150 mg-25%

Technologies	Total costs (£)	Total QALYs	LYG	Incremental costs (£)	Incremental QALYs	Incremental ICER
Standard of care without solriamfetol	£0	11.524	30.213			
Standard of care with the addition of solriamfetol	[redacted]	11.937	30.213	[redacted]	0.413	[redacted]

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

Alternative HRQoL estimates

OSA based QoL estimates from McDaid

Scenario analysis: ESS to EQ-5D McDaid 2007 regression - Combined

Technologies	Total costs (£)	Total QALYs	LYG	Incremental costs (£)	Incremental QALYs	Incremental ICER
Standard of care without solriamfetol	£0	13.963	30.213			
Standard of care with the addition of solriamfetol	[redacted]	14.304	30.213	[redacted]	0.341	[redacted]

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

OSA based QoL estimates from TTO analysis

Scenario analysis: TTO utilities - Combined

Technologies	Total costs (£)	Total QALYs	LYG	Incremental costs (£)	Incremental QALYs	Incremental ICER
Standard of care without solriamfetol	£0	12.028	30.213			
Standard of care with the addition of solriamfetol	[redacted]	12.864	30.213	[redacted]	0.836	[redacted]

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

Partner utilities

Scenario analysis: NHWS mapping combined with partner utilities

Technologies	Total costs (£)	Total QALYs	LYG	Incremental costs (£)	Incremental QALYs	Incremental ICER
Standard of care without solriamfetol	£0	20.605	30.213			
Standard of care with the addition of solriamfetol	[redacted]	21.129	30.213	[redacted]	0.524	[redacted]

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; NHWS, National Health and Wellness Survey; QALYs, quality-adjusted life years.

Scenario analysis: McDaid mapping combined with partner utilities

Technologies	Total costs (£)	Total QALYs	LYG	Incremental costs (£)	Incremental QALYs	Incremental ICER
Standard of care without solriamfetol	£0	23.943	30.213			
Standard of care with the addition of solriamfetol	[redacted]	24.410	30.213	[redacted]	0.467	[redacted]

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

Scenario analysis: TTO patient utilities combined with TTO partner utilities

Technologies	Total costs (£)	Total QALYs	LYG	Incremental costs (£)	Incremental QALYs	Incremental ICER
Standard of care without solriamfetol	£0	21.296	30.213			
Standard of care with the addition of solriamfetol	[redacted]	22.440	30.213	[redacted]	1.144	[redacted]

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

Subgroup analysis

Compliant or non-compliant to primary OSA therapy

Subgroup analysis: Compliant to a primary OSA therapy (at randomisation into TONES 3) – solriamfetol combined

Technologies	Total costs (£)	Total QALYs	LYG	Incremental costs (£)	Incremental QALYs	Incremental ICER
Standard of care without solriamfetol	£0	11.382	29.301			
Standard of care with the addition of solriamfetol	[redacted]	11.727	29.301	[redacted]	0.345	[redacted]

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

Subgroup analysis: Non-compliant to a primary OSA therapy (at randomisation into TONES 3) – solriamfetol combined

Technologies	Total costs (£)	Total QALYs	LYG	Incremental costs (£)	Incremental QALYs	Incremental ICER
Standard of care without solriamfetol	£0	11.767	32.026			
Standard of care with the addition of solriamfetol	[redacted]	12.226	32.026	[redacted]	0.459	[redacted]

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

Baseline ESS at entry

Subgroup analysis: Incremental ESS scores considered from the TONES 3 mIPD

Baseline ESS	37.5 mg	75 mg	150 mg	Weighted
≥ 10	[redacted]	[redacted]	[redacted]	[redacted]
> 10	[redacted]	[redacted]	[redacted]	[redacted]
> 12 (base case)	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: ESS, Epworth sleepiness scale; IPD, individual patient data; mIPD, modified individual patient data; OSA, obstructive sleep apnoea.

Full company response to Key Issues 4 and 7 & company response to the ERG's proposed model modifications

Placebo serves as a control arm for the TONES 3 clinical trial, but placebo is not prescribed in clinical practice. It is well documented that placebo effects occur within clinical trials and also in the real world. There are three potential components of placebo effect in a clinical trial:

1. True placebo – the benefit of taking something a patient believes to be an active treatment but which has no medicinal effects. This placebo effect would be experienced by the patient in clinical practice when the active substance is prescribed

2. Hawthorne effect – where the placebo effect is caused by the artefact of the study population being enrolled in a trial setting. This would not be seen in clinical practice

3. Regression to the mean – where the patients are considered to have been enrolled in a clinical trial at an severe point in their illness and thus there is some natural, treatment-unrelated improvement over time from the most severe point of illness to an improved state

As described below, there is strong clinical evidence that the placebo effect in TONES 3 is due to true placebo. In the CS, however, Jazz took the conservative approach and assumed the effect was attributable to the Hawthorne effect, adjusting for solriamfetol efficacy using a centring methodology which reduced the effect size in both the placebo and solriamfetol arm.

The ERG argue that the placebo effect is entirely attributable to regression to the mean and Jazz presents multiple rationales as to why the reduction in Epworth Sleepiness Scale (ESS) scores observed in the placebo arm of TONES 3 cannot be regression to the mean (see Section 1.3). In addition, the assumption of regression to the mean introduces paradoxes in the ERG's model which further translate into clinical implausibility (see Section 1.3).

Company response to the ERG's corrections to the company's model

The ERG made some corrections to the company's model (TE Report, Section 5.3.1), which included adding discontinuation rates for the standard of care arm, and editing the company's model to correct for (in the ERG's opinion) the company's assumptions that contradicted the mutual exclusivity of events when transitioning through the company model health states.

- The company note that a rate of discontinuation due to TEAEs within the standard of care without solriamfetol arm was included in error by Jazz in the company model – however, as outlined in CS B3.3.2, as a consequence of the centring exercise performed on the data by Jazz, the company model does not include discontinuation in the standard of care without solriamfetol arm, as these patients were assumed not to receive an active treatment and thus cannot discontinue 'nothing' (see "ERG model paradox" in Section 1.5).

- It is unclear what specific adjustments were made to the Markov trace formulae by the ERG, so Jazz has not made any adjustments to this in their model nor their base case analysis.

Summary of the ERG's preferred assumptions and resulting ICER in the ERG's model

In addition to the ERG corrections to the company's model outlined above, the ERG's preferred assumptions within the ERG's own model (TE Report, Section 1.4) include the following changes to the company's base-case assumptions:

1. The use of uncentred IPD from the TONES 3 mITT population to estimate treatment effect and proportion of responders (TE Report, Section 4.2.6.2)
2. Amending the model by adding a new health state for patients who discontinue solriamfetol due to AEs but are still considered responders (TE Report, Section 6.1)
3. Using discontinuation rates due to loss of response and SAEs stratified by treatment dose from TONES 5 (TE Report, Section 4.2.6.4)
4. Patient population as in TONES 3, with ESS ≥ 10 (TE Report, Section 4.2.3.1)
5. Defining treatment response as a reduction in ESS from baseline of at least 2 points (TE Report, Section 4.2.6.3)
6. The proportion of patients receiving 37.5 mg, 75 mg and 150 mg doses of solriamfetol 25:/50:/25 (TE Report, Section 4.2.8.1.2)
7. Including the cost of hospitalisation due to serious AEs in patients treated with solriamfetol (TE Report, Section 4.2.8.3.2)

Jazz's response or comment on each of these elements is outlined in further detail below.

1 The use of uncentred IPD from the TONES 3 mITT population to estimate treatment effect and proportion of responders (TE Report, Section 4.2.6.2)

1.1 Brief summary of company's model approach

The company's model incorporated a 'centring' mechanism to adjust for the placebo effect in TONES 3 and this centring exercise allowed only the incremental effects of solriamfetol for managing excessive daytime sleepiness (EDS) to be assessed in the model analyses.

Note that patients in both the solriamfetol and the placebo arms of TONES 3 were using a primary OSA therapy such as CPAP (i.e. standard of care), to manage their underlying OSA. These patients were randomised to receive either placebo or solriamfetol to manage the symptom 'EDS' (but continued to use their primary OSA therapy during the trial). In some patients with OSA, primary OSA therapies such as CPAP may reduce their EDS, however a small proportion of patients may continue to experience EDS despite optimal use of their primary OSA therapy.

In current UK clinical practice, there are no pharmacological agents licensed and indicated to manage EDS in patients with residual EDS despite primary OSA therapy. As such, if these patients presented with EDS in practice, they would not receive any additional treatment for their EDS other than their existing standard of care for the underlying OSA (i.e. primary OSA therapy, CPAP). As such, this posed a modelling challenge within the company's analysis: what should happen when patients in the standard of care without solriamfetol arm (i.e. placebo arm) 'stop' receiving treatment'? As these patients were not receiving any treatment specifically for their EDS and they cannot discontinue "nothing", the company took the

approach that patients prescribed a primary therapy and still suffering from residual EDS would, on average, not improve without a therapy being prescribed. The assumptions of regression to the mean and true placebo are extremes, and whilst the company felt there was evidence of true placebo, a conservative assumption of a Hawthorne effect was taken. The efficacy for solriamfetol was reduced via a centring exercise to adjust for this placebo effect.

1.2 Brief summary of the ERG model and regression to the mean

The ERG state that there is no direct evidence to validate the centring exercise used in the company's base case, and instead preferred to use the unadjusted TONES 3 trial data, and assumed that the efficacy seen in the placebo arm of TONES 3 was due to a regression to the mean.

Regression to the mean, occurs when there is natural variation over time in the severity of a condition and proposes that people are more likely to be recruited into a clinical trial during a particularly bad phase of their condition (i.e. a temporary worsening in the patient's status which may cause them to seek treatment or enrol in a clinical trial, following which they will naturally return to their pre-worsened, mean or average status). Regression to the mean considers that, when observing repeated measurements in the same patient, relatively high or relatively low initial observations are likely to be followed by less extreme values nearer the patient's true mean status.

Whilst Jazz recognise the ERG's rationale for using the unadjusted data (that it best reflects the 12-week trial period of TONES 3), Jazz also note that:

- there are substantial limitations in utilising this 12 week data in the long-term analysis of the standard of care without solriamfetol arm
- there is no direct evidence to support the ERGs preferred assumption in the long-term

1.3 Examining the evidence for a placebo effect

Based on the ERG's challenge on Jazz's approach to placebo effect, considerable further analysis was performed to examine the evidence for true placebo, Hawthorne effect, and regression to the mean, and assess the most appropriate way to adjust for the placebo effect in TONES 3.

1.3.1 TONES trial evidence contradicting regression to the mean

1.3.1.1 Evidence based on patients moving from TONES 4 into TONES 5

A total of 83 patients transitioned from TONES 4 into the long term TONES 5, and this group of patients thus had a baseline ESS measured at the beginning of both trials. Importantly, after completing TONES 4 but before starting TONES 5, these patients were not receiving any treatment, neither solriamfetol nor placebo. Figure 1 below demonstrates that at baseline of both trials, the ESS scores for these patients are within ~1 point of each other, indicating the baseline value is their 'true' mean ESS. The change in ESS scores in these 83 patients as treated with solriamfetol (all timepoints, with the exception of a 2 week randomised withdrawal period in TONES 4) – for clarity, the randomised withdrawal period in

TONES 5 is not shown. The reduction in ESS scores at the beginning of TONES 4 and TONES 5 is consistent with the rapid rate of solriamfetol effect seen in TONES 3 (see Figure 2 and Figure 3 CS B.2.6.1.2).

Figure 1. Visual plot of baseline value and change from baseline

Study TONES 4 is TONES 4 (2 week titration, 2 week stable dose, 2 week randomised withdrawal)
Study TONES 5 is TONES 5 (long-term open label extension study)
Patients from TONES 4 had a break in treatment of unknown duration before starting TONES 5.

As shown in Figure 1, in TONES 4, patients received the majority of their ESS improvement during the initial 2 week titration period, with the benefit staying broadly constant during the subsequent 2 week stable dose period; ESS score increased upon discontinuing solriamfetol treatment and transitioning into TONES 5, but at the first time point assessed in TONES 5 (week 2) their ESS had reduced back down to a similar level as they achieved in TONES 4, and subsequently remaining stable with very minimal variation through to the end of TONES 5. This is a recurring effect throughout the TONES trial programme. There are very small changes in ESS when the patients' status (on or off treatment) is stable but substantial changes in ESS occur rapidly when patients initiate treatment, switch from placebo to solriamfetol (or vice versa), or discontinue treatment.

The randomised withdrawal element of TONES 4 provides evidence of a substantial true placebo effect (see Section 1.4), wherein patients randomised from a stable dose of solriamfetol onto placebo experienced an increase in ESS from a score of 5.4 on solriamfetol to 10.6 on placebo and then subsequently report an ESS of 15.6 at the baseline of TONES 5 following a period without solriamfetol treatment. Note that patients in TONES 4 randomised to continue solriamfetol in the randomised withdrawal phase maintained their low ESS to the end of TONES 4 but subsequently returned to a baseline ESS of 14.2 at the baseline of TONES 5, following a period without solriamfetol treatment.

1.3.1.2 TONES trials: Screening and baseline measurements evidence

There is a small subset of patients for whom both a screening and a baseline ESS score are available. Table 1 shows that for 10 patients in TONES 3 with both ESS measurements, mean ESS was 14.6 at screening and 15.5 at baseline. For 14 patients in TONES 4 with both ESS measurement, the ESS was 15.2 at screening and 15.6 at baseline. Similar to the evidence in Figure 1 above for the subset of patients moving from TONES 4 into TONES 5, these ESS scores lie within ~1 point of each other; thereby not providing evidence of regression to the mean in the TONES trials.

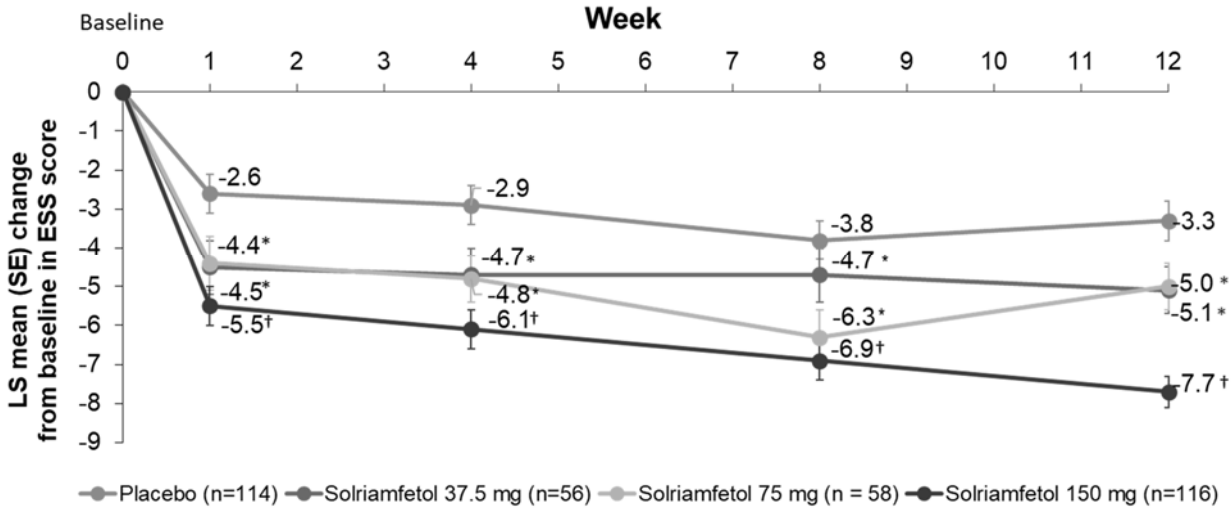
Table 1. Summary of ESS scores between baseline and screening in Subjects from Studies TONES 3 and TONES 4, and Subjects Continued to TONES 5

	TONES 3 (N=475)	TONES 4 (N=174)	TONES 5 (N=398)
ESS Score: Summary of Observed Value at Screening and Baseline by Visit			
n	[redacted]	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]	
Median	[redacted]	[redacted]	
Range	[redacted]	[redacted]	
Baseline of the Subjects having Screening Visit			
n	[redacted]	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]	
Median	[redacted]	[redacted]	
Range	[redacted]	[redacted]	
Baseline of all Subjects			
n	[redacted]	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]	[redacted]
Median	[redacted]	[redacted]	[redacted]
Range	[redacted]	[redacted]	[redacted]

1.3.1.3 Speed of response, consistency of response & lack of variability post response

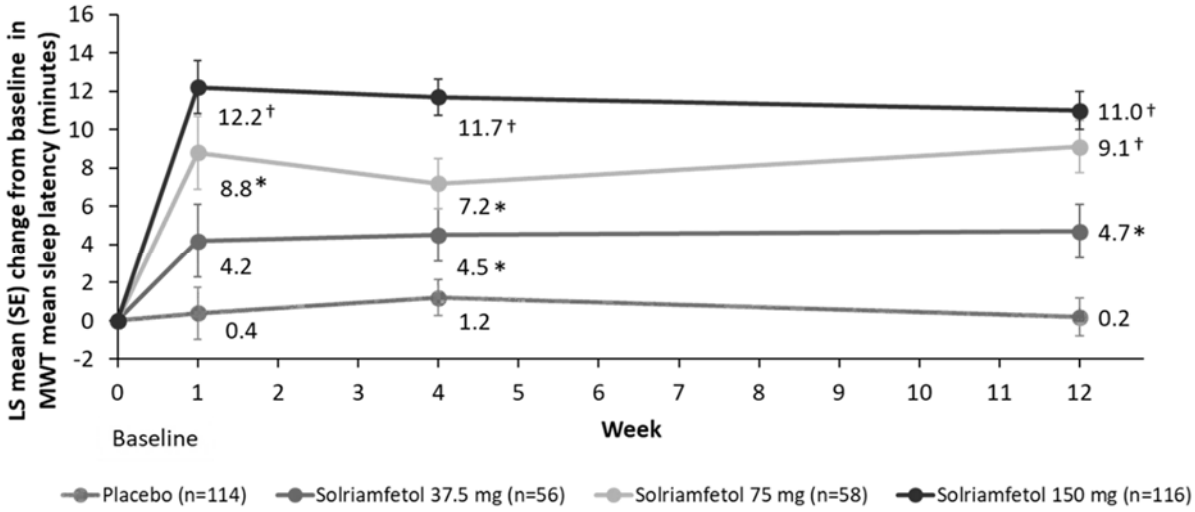
As described above, the effect of solriamfetol treatment observed at the start of TONES 3, 4 and 5 was rapid, occurring within 1-2 weeks (depending on the time point of first measurement in the respective trial). If regression to the mean were responsible for changing ESS scores, it would likely occur over a longer period of time, and it is highly unlikely that the vast majority of this regression to mean effect would happen in the first two weeks of a clinical trial; this is particularly unlikely to reflect a regression to the mean given the length of time it would take for a patient to feel that their residual EDS was having an impact on their lives, then make the decision to enrol in a clinical trial, and subsequently undergo screening and finally receive either solriamfetol or placebo. In TONES 3, patients achieved the majority of their effects during week 1, with very minimal change thereafter through week 12 (Figure 2 and Figure 3).

Figure 2: TONES 3: 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. MMRM model with change from baseline as response variable and fixed effect of treatment, visit, treatment by visit, randomisation factor and covariate of baseline value.

Figure 3: TONES 3: Change from baseline in MWT sleep latency at weeks 1, 4, and 12 (mITT Population)



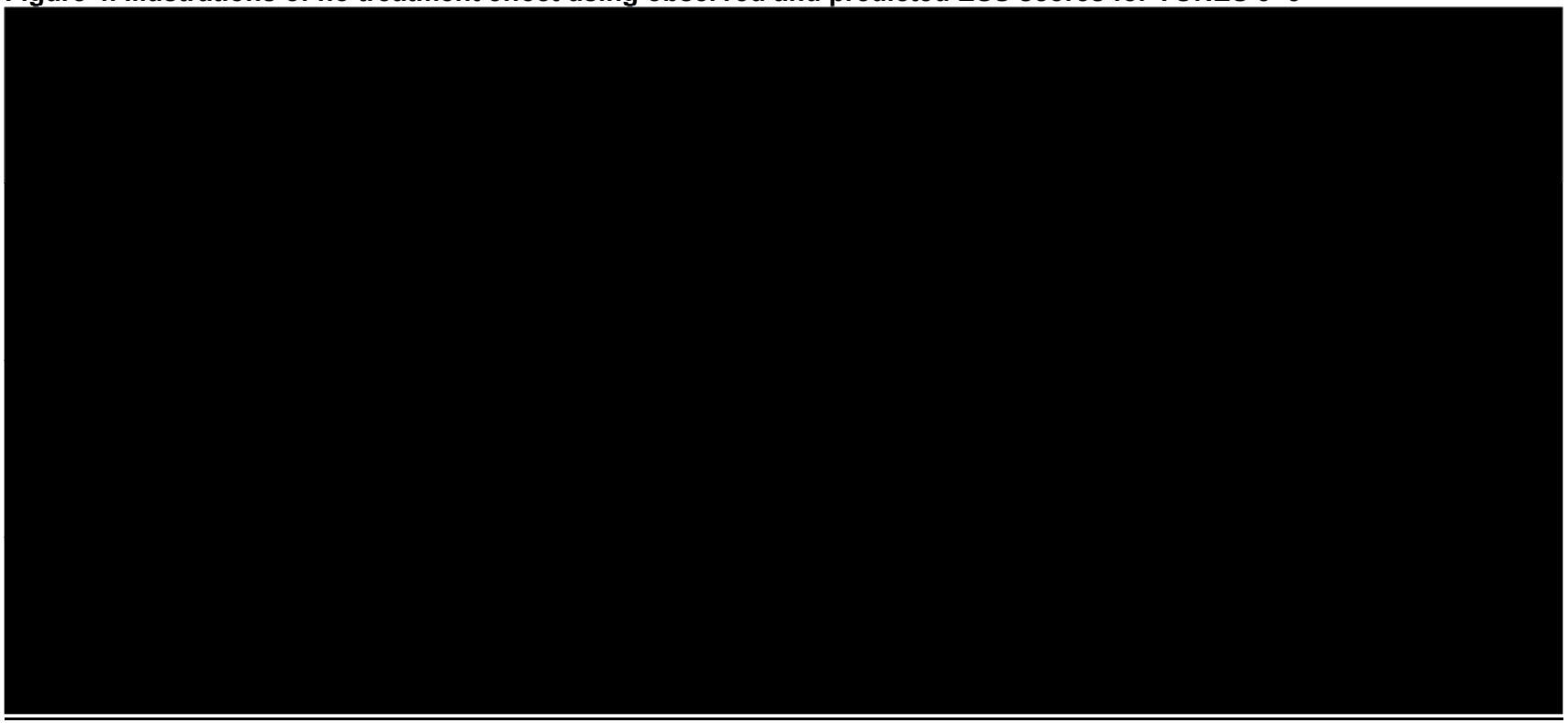
Abbreviations: CSR, clinical study report; LS, least squares; mITT, modified intent to treat; MMRM, mixed effects repeated measures; MWT, Maintenance of Wakefulness Test; SE, standard error; TONES, Treatment of Obstructive sleep apnoea and Narcolepsy Excessive Sleepiness.
*p<0.05, †p<0.0001 vs. placebo. MMRM model with change from baseline as response variable and fixed effect of treatment, visit, treatment by visit, randomisation factor and covariate of baseline value.

1.3.1.4 Exploratory analysis of combined T3-4-5 dataset

A more complex methodology was explored of bringing together the patient level data from TONES 3-4. Combining the three TONES (3,4,5) studies, a repeated measures model was fitted to ESS on the natural scale (a generalized linear model with random subject level intercepts and slopes). Baseline response was taken to be the first ESS measurement for each subject, and then elapsed time in days was calculated for the whole trajectory of each subject as they entered and left each study. Covariates included were time as a factor variable, baseline compliance status, and baseline ESS. Subjects were assumed to be taking no treatment during the gap between the TONES 4 study and the TONES 5 study. Subjects moving between the TONES 4 and TONES 5 study provided a TONES 5 screening ESS value which was then taken to represent the aforementioned period on no treatment. This "no treatment" ESS response was excluded for any subjects with a time gap of greater than 90 days.

This analysis suggests that patients treated with no treatment are likely to remain at a similar level to baseline, whilst those on solriamfetol are likely to move into the 'normal' range, with placebo somewhere in between.

Figure 4. Illustrations of no treatment effect using observed and predicted ESS scores for TONES 3–5



1.3.2 Real world evidence contradicting regression to the mean

It is important to understand whether or not any regression to the mean effects would occur in a real world setting, however this is difficult to fully measure, as it is important to understand that a change in ESS is not due to a change in treatment or lifestyle. As part of research efforts to better understand the burden of illness in patients with residual EDS, Jazz conducted a qualitative burden of illness study in 15 patients in the UK, Germany and Spain with a similar inclusion criteria to TONES 3 (19). The time period between screening and baseline was an average of 4.3 days, which is short enough that it can be reasonably assumed that neither treatment nor lifestyle changed substantially in this period. In this data set, the mean ESS at screening was 14.3 compared with 14.5 at the time of the qualitative interview, and consistent with 1.3.1.2 above, provides no evidence of a regression to the mean effect in a small but real world population. This lack of change when no treatment changes are made contrasts with the rapid effect of solriamfetol and placebo during the first week of treatment in TONES 3 and at week 2 in TONES 4 (the first time point measured).

In addition, this is supported by post ERG Report Clinical Practice Interviews in which clinicians report that ESS has been demonstrated to be reproducible over time, relatively stable over time and no clinicians reported that patients would naturally improve over time without therapeutic intervention (1).

Examining change from baseline versus baseline

Another piece of evidence that can be examined is plots of baseline ESS versus change in ESS from baseline. Here it can be seen that there is no consistent trend (Figure 5 and Figure 6) thereby not providing evidence of regression to the mean. Quantifying Regression to the Mean from TONES 3 using the methodology suggested by Barnett 2005 (20) a regression to the mean of 0.497 points.

Figure 5. Change from baseline versus baseline by week and Dose - Compliant

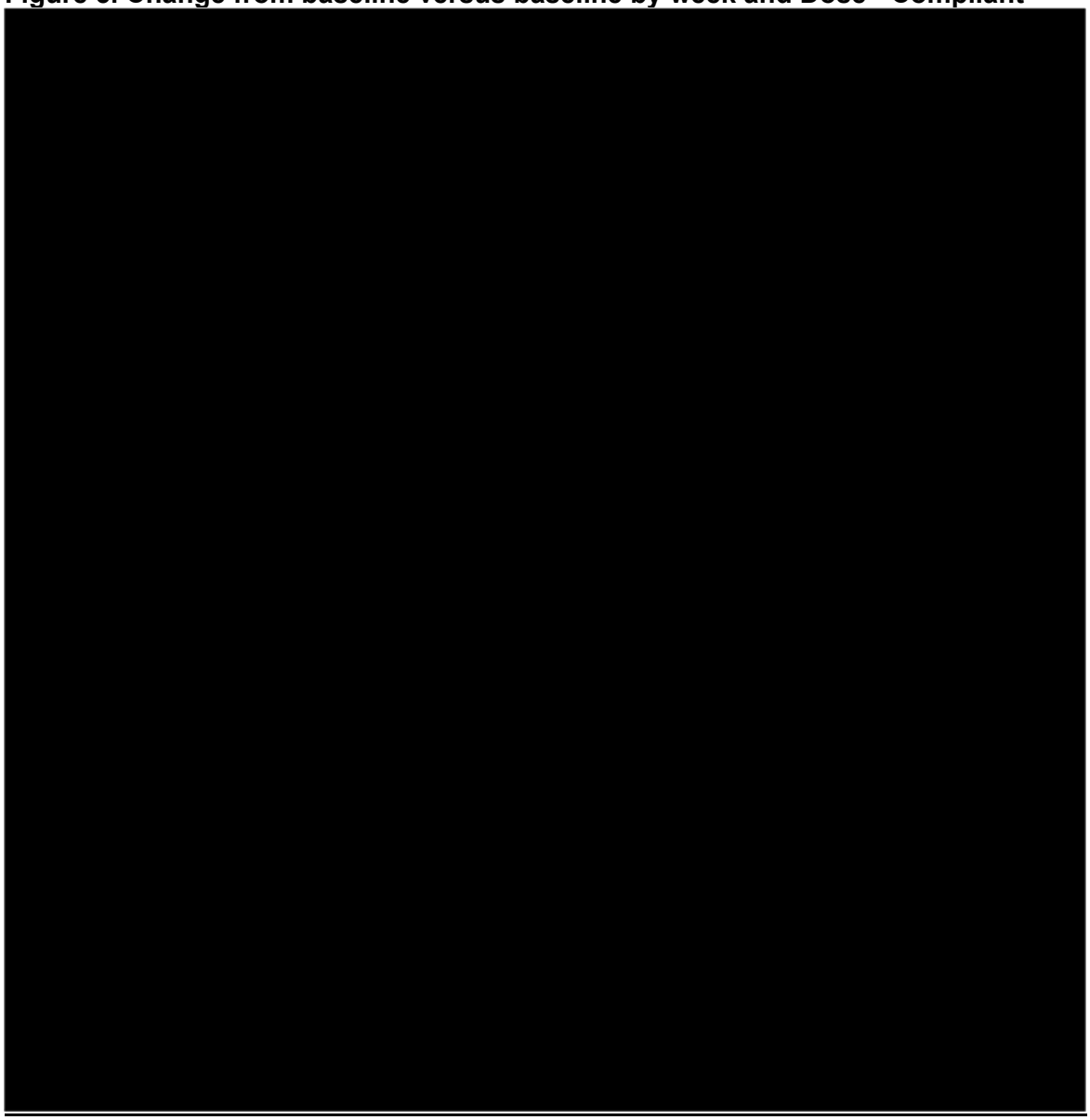
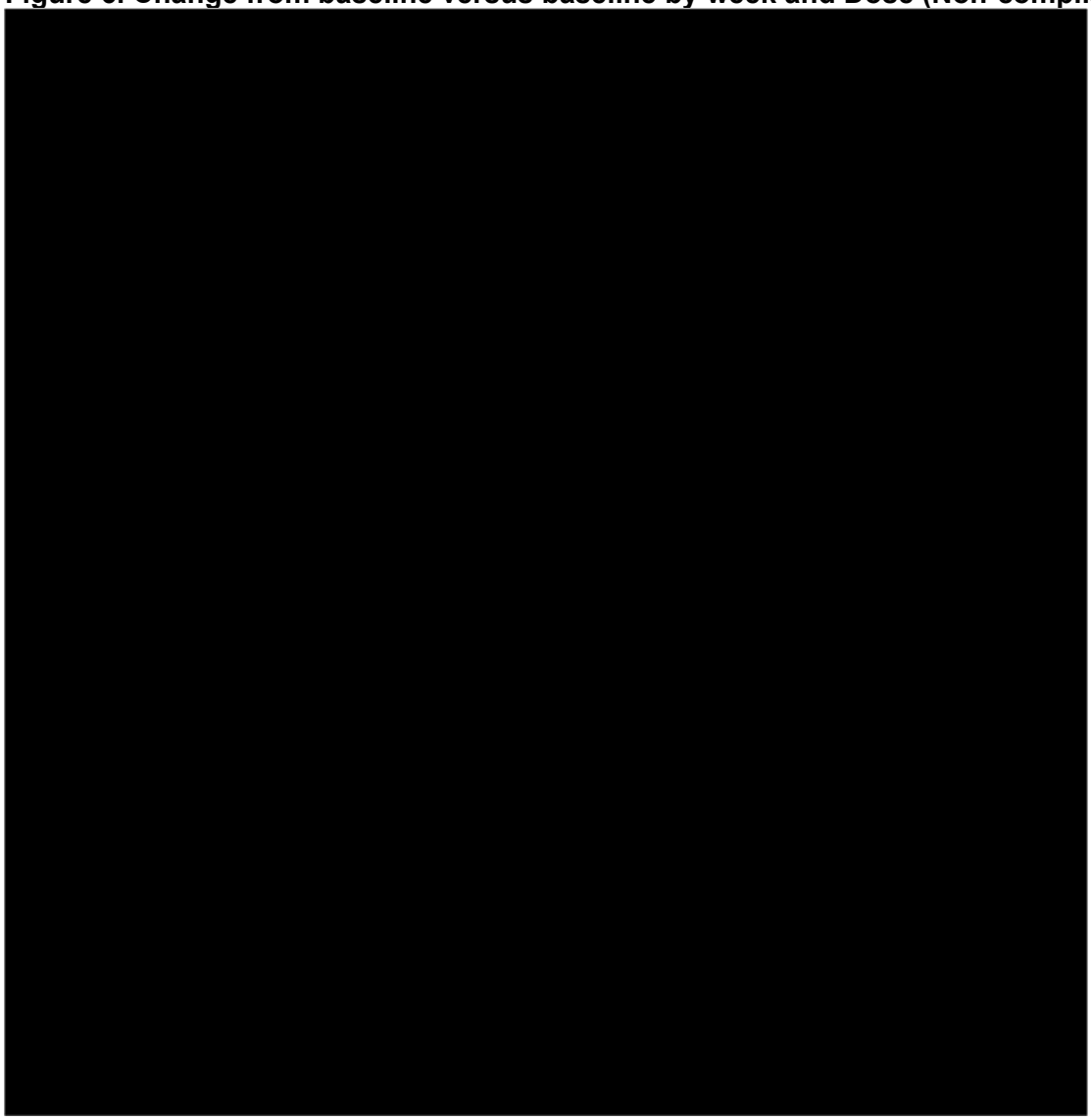


Figure 6. Change from baseline versus baseline by week and Dose (Non-compliant)



1.3.3 Clinical Practice Evidence contradicting regression to the mean

Patients with residual EDS are at the end of a long clinical diagnosis journey which has included recognition of EDS, lifestyle changes, treatment with a primary therapy and multiple consultations to rule out other causes of their residual EDS. A physician is highly unlikely to treat a patient with a wake promoting agent (WPA) at their first visit post CPAP initiation – instead patients are likely to undergo several visits to adjust their CPAP or primary OSA therapy and achieve optimal effect. If the patient had improved during this period this is likely to delay the time to initiation of a WPA. In the unlikely event that the condition of a patient who had been stable on CPAP for some time improved by an equivalent amount as seen in the placebo arm of TONES 3 without any further intervention, it is unlikely they would receive a WPA at all; at minimum, they would be further monitored.

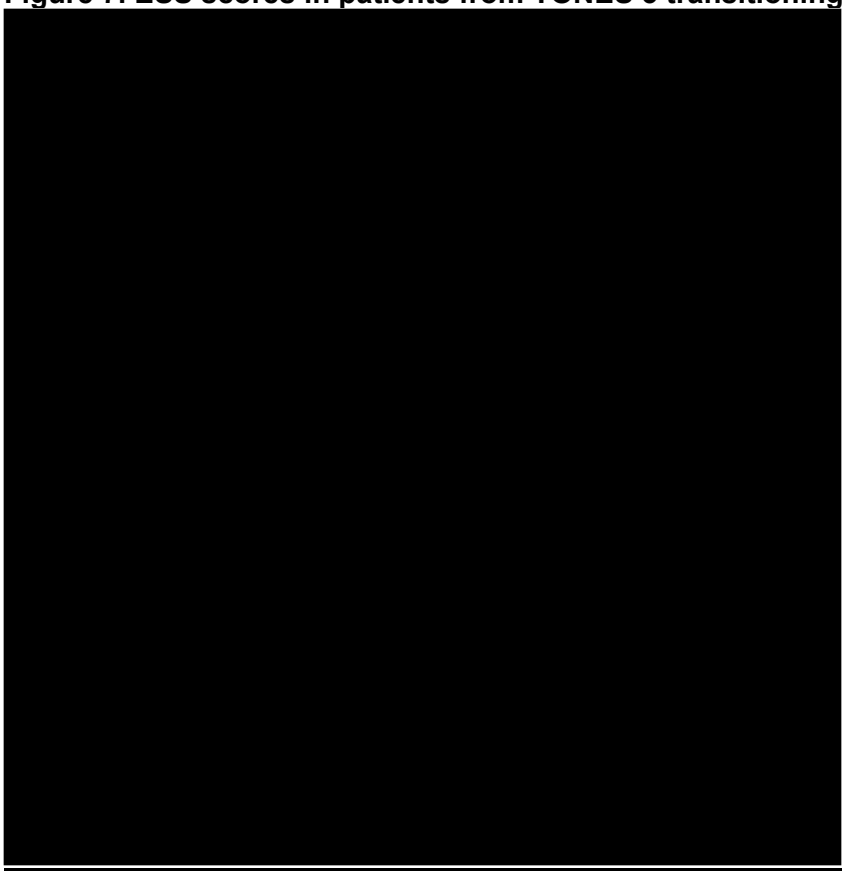
1.4 Evidence of a true placebo effect in the TONES trials

The peer-reviewed publication on TONES 5 (Malhotra 2020 (21)) proposes that the effects observed in the randomised withdrawal (RW) phase of TONES 5 support a true placebo effect: "*The RW phase also provides evidence that improvements observed in this study are not simply related to changes that might have occurred over time (e.g. a resolution of symptoms) and that the beneficial effects observed with solriamfetol are not likely to be related to placebo or Hawthorne effects from being in the trial. In addition, there were no signs of rebound effects or withdrawal after long-term use of solriamfetol.*"

Figure 1 shows that in the TONES 4 randomised withdrawal study, patients who had previously achieved an ESS reduction with solriamfetol, experienced an increase to an ESS of 10.6 when randomised to placebo, before subsequently returning to an ESS of 15.6 after discontinuing solriamfetol; this could not be a result of either Hawthorne effect or regression to the mean and therefore this likely a true placebo effect.

When patients transition from TONES 3 to TONES 5 (Figure 7), patients treated with solriamfetol improve when their treatment is unblinded, suggesting a further effect from the certainty of knowing their EDS is being managed with active treatment. Figure 7 also shows that as patients previously receiving blinded placebo are switched to open label solriamfetol, their already meaningful reduction in ESS due to the placebo effect achieves a substantial further improvement with solriamfetol treatment. This additional benefit brings patients to similar mean ESS as those patients treated with blinded solriamfetol in TONES 3 and whose treatment is unblinded in TONES 5. This provides further evidence that the effect of the placebo arm in TONES 3 is true placebo, as these patients were able to improve even further with their solriamfetol treatment, and indicates that the company's centring exercise is conservative.

Figure 7. ESS scores in patients from TONES 3 transitioning into TONES 5



1.5 The ERG model paradox

In light of the modelling challenge posed by the standard of care without solriamfetol arm (what should happen when patients in the standard of care without solriamfetol arm (i.e. placebo arm) 'stop' receiving treatment, as they cannot discontinue "nothing"), the ERG's use of the uncentred IPD from TONES 3 introduces a methodological paradox into their proposed model structure, and furthermore, it contradicts the available clinical evidence for solriamfetol. Whereas in the TONES 3 trial, the control group (receiving placebo) could legitimately consider that they could have been receiving an active substance through randomised blinding. In clinical practice the standard of care patients would have no such underlying placebo-effect, having had no additional intervention or treatment. There is therefore no interventional effect to withdraw. Conversely, patients treated with solriamfetol could be expected to benefit from a treatment effect similar to patients in the open-label TONES 5 trial, where the subjects knew that they were receiving an active substance. The holistic treatment effect of both the pharmacological effect of the medicine, as well the cognitive effect of knowing that a treatment has been initiated and maintained, can be expected in the solriamfetol arm of the model, but not the standard of care arm.

If the reduction in ESS achieved in the placebo arm of TONES 3 is due to a regression to the mean, then their ESS in response to placebo would represent the "true mean" ESS for patients receiving placebo in the model (i.e. standard of care without solriamfetol – no active

treatment for EDS). Despite this assumption that the placebo arm ESS score reflects regression to the mean, the ERG model still allowed patients receiving placebo (i.e. standard of care) to discontinue treatment ('nothing') and in those patients who discontinued, their ESS score was able to increase (indicating worse levels of sleepiness) and in doing so, to move away from the implied "true mean".

In clinical practice, patients on standard of care, such as CPAP, will not receive an active treatment specifically for EDS and so there is nothing to physically discontinue. The ERG assumed that patients receiving placebo will discontinue 'nothing' at a weighted mean rate of discontinuation (based on the solriamfetol arms of TONES 3) but without providing clinical justification for this assumption.

The patients that discontinue standard of care without solriamfetol will return to their baseline ESS score, but if the improvement in ESS for those on standard of care without solriamfetol is due to a regression to the mean, then the ERG's assumption that the ESS will change over time upon discontinuation contradicts the ERG's initial assumption that the original improvement in ESS from baseline within the placebo arm was due to a regression to the mean. The ERG's assumptions are therefore mutually exclusive, yet both are applied.

Within the ERG analysis, Table 36 considers the cumulative impact of the ERG's preferred scenarios. In the ERG scenario which removes the centring exercise for the placebo effect, the analysis shows that solriamfetol becomes dominated by standard of care without solriamfetol (i.e. there are fewer QALYs associated with solriamfetol than standard of care alone, and the inclusion of solriamfetol is more expensive).This is counterintuitive as it provides an outcome where giving an active treatment (clinically demonstrated as superior to placebo in TONES 3) would result in fewer QALYs within the context of the model. This implausible outcome occurs simply because of the contradicting assumptions made by the ERG (i) the assumption that efficacy in the standard of care without solriamfetol arm is due to a regression to the mean and will persist indefinitely vs (ii) the assumption that those on solriamfetol who discontinue solriamfetol will revert to baseline ESS score.

To counter this implausible outcome, the ERG incorporate a fourth health state into their model, for patients who discontinue solriamfetol but are still considered responders. To introduce this fourth health state the ERG are required to make two assumptions (i) on the proportion of discontinuers who still respond and, (ii) the level of response that these discontinuers will persist at. This contradicts the clinical data previously described which shows that following extended periods of solriamfetol discontinuation patients will revert to their baseline ESS score (i.e. their ESS score when using primary OSA therapy to manage their underlying OSA).

Despite the addition of this fourth health state, if the effect of modifying the discontinuation of 'no treatment' in the ERG model is examined, it continues to produces a series of paradoxical findings:

- If this setting is set to zero as might be expected for 'no treatment', 'no treatment' dominates solriamfetol. This is implausible for a symptomatic treatment where patients and physicians know within a period of days if the patient is responding, and where if the effect stops when patients discontinue. There is no evidence to suggest that solriamfetol is worse than 'no treatment'

- Although this scenario is considered implausible, hypothetically if it were possible to discontinue 'no treatment', it might be expected that 'nothing' would be worse than an active treatment and suffer a higher 'lack of efficacy' (noting that lack of efficacy occurred in only 4 patients treated with 75 mg in TONES 5 and 2 patients treated with 150 mg) therefore discontinuation due to a lack of efficacy would be expected to be higher on 'no treatment' than an active arm of the trial. However the ERG assumed the average rate of discontinuation for 'no treatment' would be the average of the active solriamfetol rates. It should be noted that discontinuation rates of less than around 6% result in the two lower doses of solriamfetol being dominated by 'no treatment' (i.e. standard of care) which would indicate that for these highly burdened patients, doing nothing to manage their EDS is better than doing something.

- The ERG model is highly sensitive to this 'no treatment' discontinuation rate. Any modelling scenario which requires 'no treatment' to be discontinued cannot reflect clinical practice. This requirement in the ERG model for patients to discontinue 'no treatment' implies this approach to be inappropriate for this decision problem.

1.6 Conclusion

Following extensive examination of the TONES programme, there is strong evidence to indicate that the predominant element of placebo within the TONES programme is the true placebo effect. There is little evidence to support the presence of a Hawthorne effect with the bulk of evidence suggesting that the placebo effect seen in TONES 3 is most likely a true placebo effect, however despite this, Jazz took a conservative position and applied a Hawthorne effect in the company model. Additionally Jazz have presented substantial evidence to demonstrate there is no meaningful contribution from regression to the mean.

The company is retaining its Hawthorne (i.e. centring exercise) adjusted base case (ICER £[redacted], PSA suggesting a 62% and 99% probability of being cost effective at an ICER of £20k and £30k per QALY, respectively) with a scenario of the added benefit potential assuming a true placebo effect (ICER £[redacted]), PSA suggesting an 84% probability of being cost effective at an ICER of £20,000 per QALY, increasing to 100% at £30,000 per QALY.

2 Amending the model by adding a new health state for patients who discontinue solriamfetol due to AEs but are still considered responders (TE Report, Section 6.1)

The company model included three health states: Responder, non-responder, dead.

The ERG model included a fourth health state (Responder with no EDS treatment) - this directly conflicts with the clinical data (described above) showing that following extended periods of solriamfetol discontinuation patients will revert to their baseline ESS score (i.e. their ESS score when using primary OSA therapy to manage the underlying OSA). Furthermore, solriamfetol is not disease-modifying for the underlying cause of OSA and solriamfetol has a half-life of 7.1 hours.

For these reasons, the company base case analysis assumed that solriamfetol treatment effects diminished rapidly upon solriamfetol discontinuation, and patients returned to their baseline score (i.e. their ESS score when using primary OSA therapy).

Jazz believe that this fourth health state introduced by the ERG is only necessary in the ERG's model to account for the inconsistencies that arise from the ERG's assumption that the efficacy in the standard of care without solriamfetol arm is due to a regression to the mean. Furthermore, the introduction of the fourth health state does not eliminate the potential implausible scenario where solriamfetol treatment can be worse than 'no treatment'.

3 Using discontinuation rates due to loss of response and SAEs stratified by treatment dose from TONES 5 (TE Report, Section 4.2.6.4)

Jazz agree with the ERG's application of discontinuation rates for AEs, and have applied this approach in the company's revised base case analysis (Full cost effectiveness analysis at PAS price and updated model assumptions).

4 Patient population as in TONES 3, with ESS ≥ 10 (TE Report, Section 4.2.3.1)

Per the response to **Key issue 2**, the company base case has been amended to ESS > 12.

5 Defining treatment response as a reduction in ESS from baseline of at least 2 points (TE Report, Section 4.2.6.3)

A reduction of 2–4 points in ESS is reported to be a clinically relevant change however based on UK KOL Evidence achieving a pre specified absolute reduction in ESS is not the only method for assessing treatment response - if the patient self-reports a positive impact of treatment on their EDS or daily function, in this situation, any ESS reduction may be considered clinically meaningful, and ESS is typically assessed with clinician judgement.

In practice, the level of ESS response accepted as the threshold for response will depend on the individual patient characteristics, baseline status, the impact of EDS on their daily function, and any other individual factors that may impact their sleepiness. For example, a person may report a substantial improvement in their daily function and usual activities despite achieving only a small ESS reduction, and it can be assumed that the benefit to QoL

will be greater for this person, compared with a person who experiences a high ESS reduction but reports no effect on their daily function or usual activities.

Given the wide variation in UK practice and across individual patients in the threshold of ESS that may define a response, Jazz chose the midpoint of the values reported in the literature and by KOLS (ESS=3), and used scenario analyses to assess the impact of a response defined as 2 or 4 point reduction. The ERG's definition of 2 points likely includes a greater proportion of responders, due to the less stringent threshold value, but is not necessarily more appropriate than the threshold of 3 points. As an ordinal scale, the minimally important clinical difference (MICD) in ESS lies between 2 and 3 points change (see **Key issue 3**). This is the level of improvement in EDS that would be apparent to a treated patient (16), the level of change that would need to occur for the patient to feel better. An analysis by Lammers 2019 (22), suggests that an ESS proxy for patients feeling a difference (anchored to global impressions of change, CGI-C and PGI-C ratings) in the TONES 2-5 trials (including both narcolepsy and OSA patients) is likely to be near 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.

6 The proportion of patients receiving 37.5 mg, 75 mg and 150 mg doses of solriamfetol [redacted] (TE Report, Section 4.2.8.1.2)

Per company response to Key Issue 9, the company base case remains 40/40/20 (a 2:2:1 dose split for 37.5, 75 and 150 mg doses after initial titration of solriamfetol treatment).

7 Including the cost of hospitalisation due to serious AEs in patients treated with solriamfetol (TE Report, Section 4.2.8.3.2)

Per company response to Key Issue 8, Jazz agree with the ERG position that trial data with respect to adverse event management would not necessarily apply to English clinical practice

The ERG note that according to clinical input, AE-related hospitalisations in patients treated for EDS due to OSA are relatively rare in UK practice. Despite this the ERG have chosen to use the significantly higher non-elective long stay costs rather that the non-elective short stay costs (or a combination of the two).

HRG codes for hospital admissions

Currency code	Currency description	National average unit cost Non-elective long stay	National average unit cost Non-elective short stay
DZ18D	Sleep Disorders Affecting Breathing, with Interventions, with CC Score 4+	£5,153	£1,384
DZ18E	Sleep Disorders Affecting Breathing, with Interventions, with CC Score 0-3	£2,136	£737

Further to this, the ERG note that there were instances of SAEs requiring inpatient hospitalisation or prolonging the existing hospitalisation. While it is acknowledged that several patients were hospitalised during the course of TONES 5, only one of the events identified by the ERG in TONES 5 were deemed to be in relation to the study drug (see Key issue 8)

Hospitalisation due to serious AEs

Page number/location	Subject ID	System Organ Class/ Preferred Term/ Verbatim Term	Onset phase	Actual Dose Level (mg)	Relation to study drug
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Page number/location	Subject ID	System Organ Class/ Preferred Term/ Verbatim Term	Onset phase	Actual Dose Level (mg)	Relation to study drug
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Source: CONFIDENTIAL. Jazz Pharmaceuticals TONES 5 CSR End of text safety tables.pdf

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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

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

PAS ICER Appendix O to ID1499 Document B

Company evidence submission

11th February 2021

File name	Version	Contains confidential information	Date
ID1499_Solriamfetol_PASICER_ AppendixO_Redacted	1.0	Yes	11 Feb 2021

O. Appendix O: Additional cost-effectiveness analyses

Appendix O is a new addition to the CS therefore table and figure numbers are continuous to the existing numbering in the original CS Appendix document.

O.1 Revised company base case, with solriamfetol PAS price

The results below reflect Jazz's revised base case at the time of the company's response to technical engagement (5 Feb 2021), and include modifications to the assumptions that were presented in the original CS Form B, 17 Dec 2020.

Table 54. Assumptions for revised company base case with solriamfetol PAS price

New assumptions	Unchanged assumptions
o PAS price of [redacted] per 75 mg table and [redacted] per 150 mg tablet o A revised form of the NHWS mapping algorithm which now utilizes the UK weighting scores o The ERGs preferred estimates of discontinuation due to loss of efficacy and adverse events for solriamfetol – Note that with the centred IPD discontinuation in the standard of care arm is not applicable. o Baseline ESS score of >12	o Centred IPD (Adjusting both solriamfetol and placebo/standard of care arms for the Hawthorne effect so that only the incremental benefit of solriamfetol is considered) o A 40/40/20 dose split between 37.5 mg/75 mg/150 mg o Response equal to a reduction in ESS of 3 or more

Abbreviations: ERG, evidence review group; ESS, Epworth Sleepiness Scale; IPD, individual patient-level data; NHWS, national health and wellness survey; PAS, patient access scheme.

Table 55. Summary of variables applied in the economic model

Variable	Value	Measurement of uncertainty and distribution: CI (distribution)
Discount rate: Costs	3.5%	0.0% - 6.0% (Not varied)
Discount rate: Outcomes	3.5%	0.0% - 6.0% (Not varied)
Average age at baseline	[redacted]	[redacted]
Proportion of cohort that are female	[redacted]	[redacted]
Solriamfetol - 75 mg: Pack size	28.0	28.0 - 28.0 (Not varied)
Solriamfetol - 150 mg: Pack size	28.0	28.0 - 28.0 (Not varied)
Solriamfetol - 75 mg: Pack price	[redacted]	[redacted]
Solriamfetol - 150 mg: Pack price	[redacted]	[redacted]
ESS => EQ-5D: McDaid - Constant	0.893	0.836 - 0.949 (Normal)

Variable	Value	Measurement of uncertainty and distribution: CI (distribution)
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)
Discontinuation - LoE (Year 1): solriamfetol 150 mg	[redacted]	[redacted]
Discontinuation - LoE (Year 1): solriamfetol 75 mg	[redacted]	[redacted]
Discontinuation - LoE (Year 1): solriamfetol 37.5 mg	[redacted]	[redacted]
Discontinuation - LoE (Year n): solriamfetol 150 mg	[redacted]	[redacted]
Discontinuation - LoE (Year n): solriamfetol 75 mg	[redacted]	[redacted]
Discontinuation - LoE (Year n): solriamfetol 37.5 mg	[redacted]	[redacted]
Discontinuation - TEAEs (Year 1): solriamfetol 150 mg	[redacted]	[redacted]
Discontinuation - TEAEs (Year 1): solriamfetol 75 mg	[redacted]	[redacted]
Discontinuation - TEAEs (Year 1): solriamfetol 37.5 mg	[redacted]	[redacted]
Discontinuation - TEAEs (Year n): solriamfetol 150 mg	[redacted]	[redacted]
Discontinuation - TEAEs (Year n): solriamfetol 75 mg	[redacted]	[redacted]
Discontinuation - TEAEs (Year n): solriamfetol 37.5 mg	[redacted]	[redacted]
Cost of discontinuation - TEAEs	£37	£30 - £44 (Gamma)
NHWS mapping - Constant coefficient	[redacted]	[redacted]
NHWS mapping - ESS Score: 0-11 coefficient	[redacted]	[redacted]
NHWS mapping - ESS Score: 12-14 coefficient	[redacted]	[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]
NHWS mapping - Female coefficient	[redacted]	[redacted]

Variable	Value	Measurement of uncertainty and distribution: CI (distribution)
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]
Proportion of patients receiving solriamfetol 37.5 mg	40%	20% - 60% (Dirichlet)
Proportion of patients receiving solriamfetol 75 mg	40%	20% - 60% (Dirichlet)
Proportion of patients receiving solriamfetol 150 mg	20%	0% - 40% (Dirichlet)

Abbreviations: BMI, body mass index; CCIQuan, Charlson Comorbidity Index; 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.

O.1.1 Base case results

Table 56. Base case results – weighted ICER

Technologies	Total costs (£)	Total QALYs	Total LYG	Incremental costs (£)	Incremental QALYs	ICER versus baseline (£/QALY)
Standard of care without solriamfetol	£0	11.524	30.213			
Standard of care with the addition of solriamfetol (40/40/20 37.5, 75, 150 mg)	[redacted]	11.906	30.213	[redacted]	0.383	[redacted]

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

Table 57. Base case results using the bootstrapping method – weighted ICER

Technologies	Total costs (£)	Total QALYs	Total LYG	Incremental costs (£)	Incremental QALYs	ICER versus baseline (£/QALY)
Standard of care without solriamfetol	£0	11.478	30.034			
Standard of care with the addition of solriamfetol (40/40/20 37.5, 75, 150 mg)	[redacted]	11.858	30.034	[redacted]	0.381	[redacted]

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

O.1.2 Sensitivity analyses

O.1.2.1 Probabilistic sensitivity analysis

The probability that solriamfetol would be the most cost-effective treatment at a threshold of £20,000 per QALY was 62%, and at a threshold of £30,000 per QALY, this increased to 99% (Figure 24). Across 5,000 PSA simulations, solriamfetol was associated with a mean cost of £[redacted] (95% CI: £[redacted]) and mean total QALYs of 12.236 (95% CI: 12.225, 12.247) (Table 37). These results are highly congruent with the deterministic results. Overall, the results remain consistent with the base case analysis.

Figure 24. Cost-effectiveness acceptability curve

[redacted]

Abbreviations: SoC, standard of care.

Table 58. Probabilistic sensitivity analysis results

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER incremental (£/QALY)
Standard of care without solriamfetol	£0 (£0, £0)	11.868 (11.857, 11.879)			
Standard of care with the addition of solriamfetol (40/40/20 37.5, 75, 150 mg)	[redacted]	12.236 (12.225 - 12.247)	[redacted]	0.368	[redacted]

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

O.1.2.2 Deterministic sensitivity analysis

Figure 25. Results of univariate analysis: standard of care with the addition of solriamfetol versus standard of care without solriamfetol

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

Table 59. Results of univariate analysis: standard of care with the addition of solriamfetol versus standard of care without solriamfetol

Variable (lower bound to upper bound; base case value)	ICER with lower bound	ICER with upper bound
Discount rate: Costs (0.0% to 6.0%; base case 3.5%)	[redacted]	[redacted]
NHWS mapping - ESS Score: 12-24 coeff [redacted]	[redacted]	[redacted]
Discount rate: Outcomes (0.0% to 6.0%; base case 3.5%)	[redacted]	[redacted]
Proportion of patients on Sol 37.5 mg (20.0% to 60.0%; base case 40.0%)	[redacted]	[redacted]
Proportion of patients on Sol 75 mg (20.0% to 60.0%; base case 40.0%)	[redacted]	[redacted]
NHWS mapping - ESS Score: 0-11 coeff [redacted]	[redacted]	[redacted]
Discontinuation - LoE (Year n): Sol 37.5 mg [redacted]	[redacted]	[redacted]
Discontinuation - TEAEs (Year n): Sol 150 mg [redacted]	[redacted]	[redacted]
Average age at baseline (42.4 to 64.9; base case 53.7)	[redacted]	[redacted]
No. of HCP contacts during titration - 37.5 mg (0 to 3; base case 1)	[redacted]	[redacted]

Abbreviations: ESS, Epworth Sleepiness Scale; ICER, incremental cost effectiveness ratio; LoE, loss of efficacy.
Yr n refers to years 2 and beyond.

O.1.2.3 Threshold analysis

Table 60. Results of threshold analysis: standard of care with the addition of solriamfetol versus standard of care without solriamfetol

Variable	Base case	Value to achieve ICER of:	
	(Lower bound to Upper bound)	£20,000 per QALY	£30,000 per QALY
Discount rate: Costs	3.5% (0.0% to 6.0%)	3.6%	-0.1%
NHWS mapping - ESS Score: 12-24 coeff	[redacted]	[redacted]	[redacted]
Discount rate: Outcomes	3.5% (0.0% to 6.0%)	3.4%	8.5%
Proportion of patients on Sol 37.5 mg	40.0% (20.0% to 60.0%)	41.0%	-58.3%
Proportion of patients on Sol 75 mg	40.0% (20.0% to 60.0%)	41.5%	-124.3%
NHWS mapping - ESS Score: 0-11 coeff	[redacted]	[redacted]	[redacted]
Discontinuation - LoE (Year n): Sol 37.5 mg	[redacted]	[redacted]	[redacted]
Discontinuation - TEAEs (Year n): Sol 150 mg	[redacted]	[redacted]	[redacted]
Average age at baseline	53.7 (42.4 to 64.9)	NA	NA
No. of HCP contacts during titration - 37.5 mg	1 (0 to 3)	-13	689

Abbreviations: coeff, coefficient; ESS, Epworth Sleepiness Scale; ICER, incremental cost effectiveness ratio; LoE, loss of efficacy; NHWS, National Health and Wellness Survey; QALY, quality adjusted life year; TEAE, treatment emergent adverse events.
Yr n refers to years 2 and beyond.
* Outside credible range.
† Because the other doses are varied independently these scenarios are implausible (as the total share will exceed 100%).

O.1.2.4 Scenario analysis

O.1.2.5 Alternative model time horizon

Table 61. Scenario analysis: Alternative model time horizon

Time horizon	Solriamfetol			
	37.5 mg	75 mg	150 mg	Weighted
5	[redacted]	[redacted]	[redacted]	[redacted]
10	[redacted]	[redacted]	[redacted]	[redacted]
15	[redacted]	[redacted]	[redacted]	[redacted]
20	[redacted]	[redacted]	[redacted]	[redacted]
25	[redacted]	[redacted]	[redacted]	[redacted]
30	[redacted]	[redacted]	[redacted]	[redacted]
35	[redacted]	[redacted]	[redacted]	[redacted]
40	[redacted]	[redacted]	[redacted]	[redacted]
45	[redacted]	[redacted]	[redacted]	[redacted]
50	[redacted]	[redacted]	[redacted]	[redacted]

Alternative definition of response

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

Technologies	Total costs (£)	Total QALYs	LYG	Incremental costs (£)	Incremental QALYs	Incremental ICER
Standard of care without solriamfetol	£0	11.524	30.213			
Standard of care with the addition of solriamfetol	[redacted]	11.936	30.213	[redacted]	0.412	[redacted]

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 – Combined

Technologies	Total costs (£)	Total QALYs	LYG	Incremental costs (£)	Incremental QALYs	Incremental ICER
Standard of care without solriamfetol	£0	11.524	30.213			
Standard of care with the addition of solriamfetol	[redacted]	11.851	30.213	[redacted]	0.327	[redacted]

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

True placebo response for standard of care without solriamfetol

Table 64. Scenario analysis: True placebo response for standard of care without solriamfetol

Technologies	Total costs (£)	Total QALYs	LYG	Incremental costs (£)	Incremental QALYs	Incremental ICER
Standard of care without solriamfetol	£0	11.524	30.213			
Standard of care with the addition of solriamfetol	[redacted]	12.157	30.213	[redacted]	0.633	[redacted]

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

Disaggregated results utilising bootstrapping methods

Table 65. Results of the bootstrapping analysis on the raw mIPD – dose split 40/40/20

Technology	Total costs (£)	Total QALYs	Total LYG	Incremental costs versus baseline (£)	Incremental QALYs versus baseline	ICER versus baseline (£/QALY)
Standard of care without solriamfetol	£0 (£0, £0)	11.478 (11.467, 11.488)	30.034 (29.991, 30.077)			
Standard of care with solriamfetol 37.5 mg	[redacted]	11.740 (11.730, 11.751)	30.034 (29.991, 30.077)	[redacted]	0.263	[redacted]
Standard of care with	[redacted]	11.831 (11.820, 11.842)	30.034 (29.991, 30.077)	[redacted]	0.091	[redacted]

Technology	Total costs (£)	Total QALYs	Total LYG	Incremental costs versus baseline (£)	Incremental QALYs versus baseline	ICER versus baseline (£/QALY)
solriamfetol 75 mg						
Standard of care with solriamfetol 150 mg	[redacted]	12.150 (12.138, 12.161)	30.034 (29.991, 30.077)	[redacted]	0.319	[redacted]

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

Alternative solriamfetol dose split

Table 66. Disaggregated solriamfetol results by solriamfetol dose

Technologies	Total costs (£)	Total QALYs	Total LYG	Incremental costs versus baseline (£)	Incremental QALY versus baseline	ICER versus baseline (£/QALY)
Standard of care without solriamfetol	£0	11.524	30.213			
Standard of care with solriamfetol 37.5 mg	[redacted]	11.786	30.213	[redacted]	0.262	[redacted]
Standard of care with solriamfetol 75 mg	[redacted]	11.882	30.213	[redacted]	0.358	[redacted]
Standard of care with solriamfetol 150 mg	[redacted]	12.196	30.213	[redacted]	0.672	[redacted]

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

Table 67. Alternative solriamfetol dose split: 37.5 mg -33%, 75 mg-33%, 150 mg-33%

Technologies	Total costs (£)	Total QALYs	LYG	Incremental costs (£)	Incremental QALYs	Incremental ICER
Standard of care without solriamfetol	£0	11.524	30.213			

Technologies	Total costs (£)	Total QALYs	LYG	Incremental costs (£)	Incremental QALYs	Incremental ICER
Standard of care with the addition of solriamfetol	[redacted]	11.955	30.213	[redacted]	0.431	[redacted]

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

Table 68. Alternative solriamfetol dose split: 37.5 mg -25%, 75 mg-50%, 150 mg-25%

Technologies	Total costs (£)	Total QALYs	LYG	Incremental costs (£)	Incremental QALYs	Incremental ICER
Standard of care without solriamfetol	£0	11.524	30.213			
Standard of care with the addition of solriamfetol	[redacted]	11.937	30.213	[redacted]	0.413	[redacted]

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

Alternative HRQoL estimates

OSA based QoL estimates from McDaid

Table 69. Scenario analysis: ESS to EQ-5D McDaid 2007 regression - Combined

Technologies	Total costs (£)	Total QALYs	LYG	Incremental costs (£)	Incremental QALYs	Incremental ICER
Standard of care without solriamfetol	£0	13.963	30.213			
Standard of care with the addition of solriamfetol	[redacted]	14.304	30.213	[redacted]	0.341	[redacted]

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

OSA based QoL estimates from TTO analysis

Table 70. Scenario analysis: TTO utilities - Combined

Technologies	Total costs (£)	Total QALYs	LYG	Incremental costs (£)	Incremental QALYs	Incremental ICER
Standard of care without solriamfetol	£0	12.028	30.213			
Standard of care with the addition of solriamfetol	[redacted]	12.864	30.213	[redacted]	0.836	[redacted]

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

O.1.2.6 Partner utilities

Table 71. Scenario analysis: NHWS mapping combined with partner utilities

Technologies	Total costs (£)	Total QALYs	LYG	Incremental costs (£)	Incremental QALYs	Incremental ICER
Standard of care without solriamfetol	£0	20.605	30.213			
Standard of care with the addition of solriamfetol	[redacted]	21.129	30.213	[redacted]	0.524	[redacted]

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; NHWS, National Health and Wellness Survey; QALYs, quality-adjusted life years.

Table 72. Scenario analysis: McDaid mapping combined with partner utilities

Technologies	Total costs (£)	Total QALYs	LYG	Incremental costs (£)	Incremental QALYs	Incremental ICER
Standard of care without solriamfetol	£0	23.943	30.213			
Standard of care with the addition of solriamfetol	[redacted]	24.410	30.213	[redacted]	0.467	[redacted]

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

Table 73. Scenario analysis: TTO patient utilities combined with TTO partner utilities

Technologies	Total costs (£)	Total QALYs	LYG	Incremental costs (£)	Incremental QALYs	Incremental ICER
Standard of care without solriamfetol	£0	21.296	30.213			
Standard of care with the addition of solriamfetol	[redacted]	22.440	30.213	[redacted]	1.144	[redacted]

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

O.1.3 Subgroup analysis

O.1.3.1 Compliant or non-compliant to primary OSA therapy

Table 74. Scenario analysis: Compliant to a primary OSA therapy (at randomisation into TONES 3) – solriamfetol combined

Technologies	Total costs (£)	Total QALYs	LYG	Incremental costs (£)	Incremental QALYs	Incremental ICER
Standard of care without solriamfetol	£0	11.382	29.301			
Standard of care with the addition of solriamfetol	[redacted]	11.727	29.301	[redacted]	0.345	[redacted]

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

Table 75. Scenario analysis: Non-compliant to a primary OSA therapy (at randomisation into TONES 3) – solriamfetol combined

Technologies	Total costs (£)	Total QALYs	LYG	Incremental costs (£)	Incremental QALYs	Incremental ICER
Standard of care without solriamfetol	£0	11.767	32.026			
Standard of care with the addition of solriamfetol	[redacted]	12.226	32.026	[redacted]	0.459	[redacted]

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

O.1.3.2 Baseline ESS at entry

Table 76. Incremental ESS scores considered from the TONES 3 mIPD

Baseline ESS	37.5 mg	75 mg	150 mg	Weighted
≥ 10	[redacted]	[redacted]	[redacted]	[redacted]
> 10	[redacted]	[redacted]	[redacted]	[redacted]
> 12 (base case)	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: ESS, Epworth sleepiness scale; IPD, individual patient data; mIPD, modified individual patient data; OSA, obstructive sleep apnoea.

O.2 Alternative baseline ESS scenario: ESS>10

These results reflect an alternative baseline of ESS>10 (as per the company base case in the original CS, 17 Dec 2020), but with all other assumptions in the model aligned with Jazz's revised position as at the time of the company's response to technical engagement (5 Feb 2021).

Table 77. Assumptions for alternative baseline of ESS > 10 in revised company model

New assumptions	Unchanged assumptions
o PAS price of [redacted] per 75 mg table and [redacted] per 150 mg tablet o A revised form of the NHWS mapping algorithm which now utilizes the UK weighting scores o The ERGs preferred estimates of discontinuation due to loss of efficacy and adverse events for solriamfetol – Note that with the centred IPD, discontinuation in the standard of care arm is not applicable.	o Centred IPD (Adjusting both solriamfetol and placebo/standard of care arms for the Hawthorne effect so that only the incremental benefit of solriamfetol is considered) o A 40/40/20 dose split between 37.5 mg/75 mg/150 mg o Response equal to a reduction in ESS of 3 or more o Baseline ESS score of >10

O.2.1 Results for an alternative scenario using baseline ESS >10

Table 78. Results – weighted ICER

Technologies	Total costs (£)	Total QALYs	Total LYG	Incremental costs (£)	Incremental QALYs	ICER versus baseline (£/QALY)
Standard of care without solriamfetol	£0	11.521	29.280			
Standard of care with the addition of solriamfetol (40/40/20 37.5, 75, 150 mg)	[redacted]	11.819	29.280	[redacted]	0.298	[redacted]

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

Table 79. Results using the bootstrapping method – weighted ICER

Technologies	Total costs (£)	Total QALYs	Total LYG	Incremental costs (£)	Incremental QALYs	ICER versus baseline (£/QALY)
Standard of care without solriamfetol	£0	11.609	29.644			
Standard of care with the addition of solriamfetol (40/40/20 37.5, 75, 150 mg)	[redacted]	11.909	29.644	[redacted]	0.300	[redacted]

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

O.3 Alternative baseline ESS scenario: ESS ≥10

These results reflect the ERG's preferred assumption of a baseline ESS ≥10 but with all other assumptions aligned with Jazz's revised position as at the time of the company's response to technical engagement (5 Feb 2021).

Table 80. Assumptions for ERG's preferred baseline (ESS ≥10)

New assumptions	Unchanged assumptions
o PAS price of [redacted] per 75 mg table and [redacted] per 150 mg tablet o A revised form of the NHWS mapping algorithm which now utilizes the UK weighting scores o The ERGs preferred estimates of discontinuation due to loss of efficacy and adverse events for solriamfetol – Note that with the centred IPD discontinuation in the standard of care arm is not applicable. o Baseline ESS score of ≥10	o Centred IPD (Adjusting both solriamfetol and placebo/standard of care arms for the Hawthorne effect so that only the incremental benefit of solriamfetol is considered) o A 40/40/20 dose split between 37.5 mg/75 mg/150 mg o Response equal to a reduction in ESS of 3 or more

O.3.1 Results for the ERG preferred assumption of ESS ≥10

Table 81. Results – weighted ICER

Technologies	Total costs (£)	Total QALYs	Total LYG	Incremental costs (£)	Incremental QALYs	ICER versus baseline (£/QALY)
Standard of care without solriamfetol	£0	11.594	29.276			
Standard of care with the addition of solriamfetol (40/40/20 37.5, 75, 150 mg)	[redacted]	11.867	29.276	[redacted]	0.273	[redacted]

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

Table 82. Results using the bootstrapping method – weighted ICER

Technologies	Total costs (£)	Total QALYs	Total LYG	Incremental costs (£)	Incremental QALYs	ICER versus baseline (£/QALY)
Standard of care without solriamfetol	£0	11.676	29.610			
Standard of care with the addition of solriamfetol (40/40/20 37.5, 75, 150 mg)	[redacted]	11.951	29.610	[redacted]	0.275	[redacted]

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

NICE National Institute for Health and Care Excellence

Patient expert statement and technical engagement response form

Solriamfetol for treating excessive daytime sleepiness caused by obstructive sleep apnoea

Thank you for agreeing to give us your views on this treatment and its possible use in the NHS.

You can provide a unique perspective on conditions and their treatment that is not typically available from other sources.

About this Form

In **part 1** we are asking you to complete questions about living with or caring for a patient with the condition.

In **part 2** we are asking you to give your views on key issues in the Evidence Review Group (ERG) report that are likely to be discussed by the committee. An overview of the key issues are summarised in the executive summary at the beginning of the ERG report.

The key issues in the ERG report reflect the areas where there is uncertainty in the evidence, and because of this the cost effectiveness of the treatment is also uncertain. In part 2 of this form we have included any of the issues raised by the ERG where we think having a patient perspective could help either:

- resolve any uncertainty that has been identified
  or
- provide missing or additional information that could help committee reach a collaborative decision in the face of uncertainty that cannot be resolved.
-

In **part 3** we are asking you to provide 5 summary sentences on the main points contained in this document.

If you have any questions or need help with completing this form please email the public involvement team via pip@nice.org.uk (please include the ID number of your appraisal in any correspondence to the PIP team).

NICE National Institute for Health and Care Excellence

Please return this form by **5pm** on **Friday 12 February 2021**

Completing this form

Part 1 can be completed anytime. We advise that the final draft of part 2 is completed after the expert engagement teleconference (if you are attending/have attended). This teleconference will briefly summarise the key issues, any specific questions we would like you to answer and the type of information the committee would find useful.

Please use this questionnaire with our hints and tips for patient experts. You can also refer to the Patient Organisation submission guide. **You do not have to answer every question** – they are prompts to guide you. There is also an opportunity to raise issues that are important to patients that you think have been missed and want to bring to the attention of the committee. The text boxes will expand as you type.

Important 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 want 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 15 pages.

PART 1 – Living with or caring for a patient with OSA and current treatment options	
About you	
1.Your name	Graham Hill
2. Are you (please tick all that apply):	**X**☐ a patient with OSA? ☐ a patient with experience of the treatment being evaluated? ☐ a carer of a patient with OSA? X☐ a patient organisation employee or volunteer? ☐ other (please specify):
3. Name of your nominating organisation.	Sleep Apnoea Trust Association (SATA)
4. Has your nominating organisation provided a submission? Please tick all options that apply.	☐ No, (please review all the questions below and provide answers where possible) X☐ Yes, my nominating organisation has provided a submission ☐ I agree with it and **do not wish to** complete a patient expert statement X☐ Yes, I authored / was a contributor to my nominating organisations submission ☐ I agree with it and **do not wish to** complete this statement X☐ I agree with it and **will be** completing

5. How did you gather the information included in your statement? (please tick all that apply)	**X**☐ I am drawing from personal experience. **X**☐ I have other relevant knowledge/experience (e.g. I am drawing on others' experiences). Please specify what other experience: I have been a SATA Committee member for 10 years, and Vice Chairman for 5 years. I represent SATA on the OSA Partnership Group and the Association for Respiratory Technology and Physiology Sleep Apnoea Committee. I have also attended annual or biennial conferences of ARTP, Royal College of GPs and the British Sleep Society as a SATA exhibitor, so I have had many discussions with medical professionals, manufacturers and others on OSA and sleep disordered breathing. **X**☐ I have completed part 2 of the statement **after attending** the expert engagement teleconference ☐ I have completed part 2 of the statement **but was not able to attend** the expert engagement teleconference ☐ I have not completed part 2 of the statement
Living with the condition	
6. What is your experience of living with OSA? If you are a carer (for someone with OSA) please share your experience of caring for them.	I was diagnosed with Obstructive Sleep Apnoea, and issued with a CPAP, in July 2000. However, I had experienced symptoms for several years prior to 2000, and was previously diagnosed with mild OSA, with no treatment indicated, in late 1993. Becoming accustomed to the CPAP took a few days, but since 2000 I have used my CPAP continuously, only not using it when suffering from, for example, a heavy cold, when breathing was difficult. It has been very effective, both in terms of minimising sleep disturbance, and in eliminating excessive daytime sleepiness. Bearing in mind my general health at the time of diagnosis, coupled with a family

	history of cardiac issues, CPAP has been life changing, and I have absolutely no doubt that CPAP treatment has saved my life.
Current treatment of the condition in the NHS	
7a. What do you think of the current treatments and care available for OSA on the NHS? 7b. How do your views on these current treatments compare to those of other people that you may be aware of?	Patient access to diagnosis and treatment of OSA is erratic. SATA has monitored NHS Sleep Clinic performance for many years, and though a number of excellent sleep clinics, pre-Covid, were able to diagnose and treat patients within reasonably short wait times, too many had excessive waiting times for diagnosis, and an unreasonably long interval between diagnosis, and setting patients up on CPAP treatment. In some cases this was due to CCGs failing to fully understand their obligation under NICE TA139 to provide adequate funding for clinics in their area of responsibility. In addition SATA considers that too many GPs do not fully understand OSA. In my conversations with GPs at, for example, RCGP Annual conferences, it is clear that the time in a 5-year medical degree course devoted to OSA varies between 15 minutes and an hour or so. SATA believes that the key to making much greater inroads into the more than 3 million undiagnosed OSA sufferers is greater understanding and involvement in the diagnostic pathway by the primary care sector. These views are shared by my colleagues within SATA.
8. If there are disadvantages for patients of **current NHS treatments** for OSA (for example how Solriamfetol is given or taken, side effects of treatment etc) please describe these	Solriamfetol is not a current treatment for OSA with EDS. I am not aware of its use in other conditions.

Advantages of this treatment	
9a. If there are advantages of this treatment over current treatments on the NHS please describe these. For example, the impact on your Quality of Life your ability to continue work, education, self-care, and care for others? 9b. If you have stated more than one advantage, which one(s) do you consider to be the most important, and why? 9c. Does this treatment help to overcome/address any of the listed disadvantages of current treatment that you have described in question 8? If so, please describe these.	There are no current treatments I am aware of for EDS associated with OSA which is not controlled by CPAP treatment
Disadvantages of this treatment	
10. If there are disadvantages of this treatment over current treatments on the NHS please describe these? For example, are there any risks with this treatment? If you are concerned about any potential	See previous answer

side affects you have heard about, please describe them and explain why.	
Patient population	
11. Are there any groups of patients who might benefit more from this treatment or any who may benefit less? If so, please describe them and explain why. Consider, for example, if patients also have other health conditions (for example difficulties with mobility, dexterity or cognitive impairments) that affect the suitability of different treatments	This proposed treatment is targeted at a particular group of patients. Which patients within this group who might benefit more or less is a clinical judgement.
Equality	
12. Are there any potential equality issues that should be taken into account when considering OSA and treatment? Please explain if you think any groups of people with this condition are particularly disadvantaged.	No. If approved the treatment should be offered to all eligible patients.

Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, sex, and sexual orientation or people with any other shared characteristics More information on how NICE deals with equalities issues can be found in the NICE equality scheme More general information about the Equality Act can and equalities issues can be found at https://www.gov.uk/government/publications/easy-read-the-equality-act-making-equality-real and https://www.gov.uk/discrimination-your-rights.	
Other issues	
13. Are there any other issues that you would like the committee to consider?	No

PART 2 – Technical engagement questions for patient experts	
Issues arising from technical engagement	
We welcome your response to the questions below, but you do not have to answer every question. If you think an issue that is important to patients has been missed in the ERG report, please also advise on this in the space provided at the end of this section. The text boxes will expand as you type. Your responses to the following issues will be considered by the committee and may be summarised and presented in slides at the appraisal committee meeting. For information: the patient organisation that nominated you has been sent a technical engagement response form (a separate document) which asks for comments on each of the key issues that have been raised in the ERG report, these will also be considered by the committee.	
14a. Are the comparators (the current treatment available in the NHS) in the company submission used in the NHS for treating the condition? 14b. Is the assessment tool used in the clinical trial appropriate for assessing the severity of OSA?	14a. There is no current treatment other than CPAP for EDS associated with OSA 14b. The ERG report highlighted some limitations in the CS 14c. The main benefit would be the control of EDS where it has not been possible to control EDS by means of CPAP 15.There is a real risk that compliance with CPAP treatment would decrease. CPAP treatment is very effective but is undoubtedly restrictive in use etc. A once-a-day pill which reduced or eliminated the most obvious symptom, EDS, might encourage patients to believe that CPAP itself was less beneficial. 16. That is a matter for clinical judgement. 17. A matter for clinical judgement

14c. What are the main benefits of this treatment for patients? If there are several benefits please list them in order of importance. Are there any benefits of this treatment that have not been captured? 15. What would be the effect on patient compliance with first line therapy such as CPAP if soliramfetol improved OSA symptoms? 16. What is the ESS level that best reflects 'normal' level of daytime sleepiness, and the group of patients who would most benefit from solriamfetol treatment?	

17. What would you say is the appropriate definition of treatment response, in terms of ESS reduction or other measurable factors concerned in OSA?	
15. Are there any important issues that have been missed in ERG report?	

PART 3 -Key messages

16. In up to 5 sentences, please summarise the key messages of your statement:

-
-
-
-
-

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.

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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.

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NICE National Institute for Health and Care Excellence

Clinical expert statement & technical engagement response form

Solriamfetol for treating excessive daytime sleepiness caused by obstructive sleep apnoea

Thank you for agreeing to comment on the ERG report for this appraisal, and for providing 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. The ERG report and stakeholder 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.

Information on completing this form:

- In **part 1** we are asking you to complete questions where we ask for your views on this technology. You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.
- In **part 2** we are asking you to give your views on key issues in the Evidence Review Group (ERG) report that are likely to be discussed by the committee. An overview of the key issues are summarised in the executive summary at the beginning of the ERG report.
- The key issues in the ERG report reflect the areas where there is uncertainty in the evidence, and because of this the cost effectiveness of the treatment is also uncertain. In part 2 of this form we have included any of the issues raised by the ERG where we think having a clinical perspective could help either:
- resolve any uncertainty that has been identified
  OR
- provide missing or additional information that could help committee reach a collaborative decision in the face of uncertainty that cannot be resolved.

In **part 3** we are asking you to provide 5 summary sentences on the main points contained in this document.

Please return this form by **5pm** on **12 February 2021**

Completing this form

Part 1 can be completed anytime. We advise that the final draft of part 2 is completed after the expert engagement teleconference (if you are attending/have attended). This teleconference will briefly summarise the key issues, any specific questions we would like you to answer and the type of information the committee would find useful.

Important 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 want to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Do not include medical information about yourself or another person that could identify you or the other person.
- 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.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.

PART 1 – Treating a patient with excessive daytime sleepiness caused by obstructive sleep apnoea and current treatment options	
About you	
1. Your name	**Sonya Craig**
2. Name of organisation	**British Thoracic Society**
3. Job title or position	**Consultant Sleep Physician and Chair of BTS Specialist Advisory Group for Sleep**
4. Are you (please tick all that apply):	**x**☐ an employee or representative of a healthcare professional organisation that represents clinicians? **x**☐ a specialist in the treatment of people with excessive daytime sleepiness caused by obstructive sleep apnoea? **x**☐ a specialist in the clinical evidence base for excessive daytime sleepiness caused by obstructive sleep apnoea 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)	☐ yes, I agree with it ☐ no, I disagree with it ☐ I agree with some of it, but disagree with some of it **x**☐ 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.)	☐ yes
7. Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	**None**
The aim of treatment for excessive daytime sleepiness caused by obstructive sleep apnoea	
8. What is the main aim of treatment? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability.)	To improve residual daytime sleepiness in patients with OSA where primary therapy (usually CPAP) has not improved their symptoms.
9. 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	An improvement in subjective Sleepiness score (ESS) of more than 2-3 but also accompanied by improved quality of life. For instance the patient may describe being able to work more effectively, engaging with family, feeling more energetic and more stable mood.

by a certain amount.)	
10. In your view, is there an unmet need for patients and healthcare professionals in excessive daytime sleepiness caused by obstructive sleep apnoea?	Yes, there are no options currently for the relatively small group of patients with OSA who have residual sleepiness (rEDS). However, it is important that other causes such as shift work, mental health, medication and sleep hygiene are taken into account. It is difficult to separate this from idiopathic hypersomnia without specialist tests.
What is the expected place of the technology in current practice?	
11. How is the condition currently treated in the NHS?	OSA is treated with CPAP if moderate to severe. There is increasing evidence that even patients with very mild OSA on a sleep study get symptomatic improvement with CPAP if they present to their doctor with sleep disturbance or other symptoms associated with poor sleep quality.
• Are any clinical guidelines used in the treatment of the condition, and if so, which?	Yes, NICE guidelines for CPAP in OSA TA 139 2008
• 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 current guidance is for treatment with CPAP if AHI>15 (sleep study severity moderate to severe). Below this level lifestyle changes such as weight loss are advised. However many sleep centres would try CPAP at a lower level of severity if the patient reports significant daytime symptoms or sleep disturbance. This is based on a number of UK RCT such as MOSAIC and MERGE which have shown improvement in ESS and HRQoL at much lower levels of sleepiness (MOSAIC) and sleep study severity (MERGE). Most Sleep physicians would advocate a trial of CPAP but there is some variability in reimbursement in some areas of the country. The pathway for set up and followup for CPAP in OSA is varied and maybe mainly nurse led, consultant led or physiologist led. Services will have developed the most efficient pathway based on local resources and referral rates. Referrals into Sleep centres have greatly increased over the last 5 years due to the increase in obesity. Most sleep

	centres report long waits for diagnostic tests, CPAP set up and follow up. Some centres use industry partners to follow up their patients and they don't have the resource to carry out servicing or mask management. Therefore the ability to detect rEDS may be different in some areas and there would likely be long delays to see a specialist.
• What impact would the technology have on the current pathway of care?	Potentially hugely disruptive. In general, Sleep services in the UK are profitable to their local trust but not always well resourced despite this. There are already delays in seeing consultants/sleep specialist nurses and although there is remote monitoring to help with compliance reviews this is not universal. It is not clear from the company submission how rEDS would be defined and what tests would be required prior to starting solriamfetol. Not all OSA centres have access to MWT for instance so defining the problem is an issue. For instance it could be the case that patients who don't like CPAP (but use it reasonably well) would falsely inflate their ESS to have the possibility of a drug rather than CPAP. In addition centres would have to remote monitor compliance much more closely than normal to ensure patients don't stop using their CPAP.
12. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	No this is a new technology
• How does healthcare resource use differ between the technology and current care?	At present patients with raised ESS on CPAP would have a compliance check either remotely or direct contact with download of their CPAP machine. Any mask issues or pressure changes would be instigated by the sleep physiology or technical team. Sleep studies on CPAP would be carried out to check for other causes. In some cases referral to a more specialist centre may be required with the suggestion of more complex sleep testing such as actigraphy or PSG. Consultant or nurse review would likely take place in most settings. Often compliance with CPAP is the issue or other medical conditions such as depression, chronic pain or chronic fatigue.
• In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	Most likely this would be specialist centres due to the potential need for further tests. However I am concerned that this could affect the ability of those specialist centres to perform their normal function of providing CPAP to their local population. It is very unlikely that primary care would be willing to take on prescribing of this drug and this will place a long term follow up burden on centres for prescribing and monitoring of the drug. For this reason I do not accept the cost effectiveness model stating that no additional visits or monitoring are required and this will fall to the sleep centre to monitor and follow up.

• What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	This is an unmet need and previously patients were unlikely to have had adequate investigation or follow up due to lack of resource and general underinvestment in sleep centres. The societal improvements are huge but investment in better staffing with monitoring of CPAP usage (which would improve CPAP compliance across the board and greatly improve cost effectiveness for the whole OSA population) are required. It is likely that non consultant medical staff such as specialist nurses would be required to prescribe and monitor effectiveness or specialist pharmacists similar to the ILD model. As this drug is expensive then it is likely to need to be specially commissioned which could help sleep services in general to ensure there is adequate staffing.
13. Do you expect the technology to provide clinically meaningful benefits compared with current care?	Yes, to some degree. It may also be useful for some patients who are only partly compliant with CPAP due to mental health issues. For these patients they are extremely disabled by daytime somnolence and often put on weight due to their medication, they develop OSA but due to their mental health are unable to tolerate CPAP at a level that would improve sleepiness. As a result their mental health deteriorates and they are unable to function in society and are a great burden to themselves and their families. Therefore for some groups this could be life changing.
• Do you expect the technology to increase length of life more than current care?	Generally no but in some groups such as patients with extreme somnolence due to OSA and mental health issues this could improve quality of life to the point where they are able to follow a healthier lifestyle and reduce weight and engage with other lifestyle improvement activities.
• Do you expect the technology to increase health-related quality of life more than current care?	Not to a great extent for the general OSA population. CPAP shows good levels of HRQoL improvements even in mild patients and is greatest for the sleepiest patients. However some groups may benefit greatly from this.
14. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	As described above there are some groups who cannot tolerate CPAP despite best efforts. These are mainly those with mental health issues who are extremely claustrophobic and unable to tolerate any mask. They are on medication that causes weight gain and sleepiness. Often CPAP is attempted and then discarded. It is possible that this drug with good side effect profile could benefit this population and improve mental health functioning to the point that CPAP can then be tried again. Other groups could be those with neurodegenerative conditions who tolerate CPAP poorly but are very sleepy. This could help their quality of life and potentially reduce their cognitive decline (some evidence in mouse models for modafinil and armodafinil).

The use of the technology	
15. 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.)	Generally more difficult. It is likely that small sleep centres specialising in OSA only would need to rule out other causes of EDS first which may require objective tests of sleepiness (due to the concern of patients saying they are sleepy; this is likely to be easily reversed by a face to face consultation however) not available at their centres. This may already happen in their area where they refer to the specialist sleep centre for help or it may increase the number of referrals to the specialist centre (more likely). This means that patients may have to travel for this medication and subsequent prescriptions. Taking a tablet is easier than CPAP but for most patients ensuring compliance with CPAP would be important. Therefore more compliance monitoring would be required which is unlikely to be able to be absorbed into the specialist centre workload unless this was a specialist complex sleep pathway where this additional workload was factored in. Patients will generally accept this medication if they perceive benefit but would stop if side effects are too great.
16. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	Generally patients would be expected to continue with CPAP therapy and be compliant in order to start. This does increase the workload of checking compliance in order to prescribe the drug. In addition other more complex testing maybe required to rule out other causes of daytime sleepiness. Although this should be happening currently, it is not clear how or when this happens in some sleep centres (possibly as no treatment for rEDS currently exists). It is likely that the presence of this drug could stimulate greater referrals for testing for rEDS . Patients would need blood pressure monitoring until stable on their dosing so this will require coming up to the sleep centre as primary care unlikely to take responsibility for this. Patients without improvement in ESS would be expected

	to stop.
17. 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?	Potential for greater effect in those with mental health problems.
18. 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?	Yes this is a novel drug with novel action. It is easy to take with few side effects and much improved compared with modafinil.
• Is the technology a 'step-change' in the management of the condition?	It is not clear how many patients have rEDS as they perhaps aren't investigated or looked for in the current OSA population. Therefore difficult to say if this is a step change.
• Does the use of the technology address any particular unmet need of	Yes as described. Those with health conditions that genuinely prevent them using CPAP effectively.

the patient population?	
19. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	This would not be suitable for patients with unstable cardiac conditions or high blood pressure.
Sources of evidence	
20. Do the clinical trials on the technology reflect current UK clinical practice?	Yes.
• 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?	My concern in general with rEDS studies is that we don't know how to measure it (sleepiness) effectively (ESS is subjective) and why patients have it. This makes it difficult to investigate and treat. ESS is subjective and the patients in the studies were very sleepy and I agree that the placebo effect needs to be taken into account. I would have liked to have seen some measure of cognitive function before and after to try and address what the drug is treating here?
• If surrogate outcome measures were used, do	As above. We don't know the long term implications of treating or not treating r EDS. It may be that this drug prevents cognitive decline and improves memory and higher cognitive function. This would be of great societal

they adequately predict long-term clinical outcomes?	benefit and much more so than just improving a sleepiness scale.
• Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	no
21. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	It is likely that the systematic review by the ERG found all relevant papers. However, Siccoli Sleep 2008 PMID 19014075 shows size of placebo effect on ESS and also effect sizes for HRQoL.
22. Are you aware of any new evidence for the comparator treatment(s) since the publication of NICE technology appraisal guidance TA139?	MOSAIC trial Craig et al Thorax 2012 PMID 23111478 showed 2 point improvement in ESS with CPAP even in minimally symptomatic patients and showed HRQol changes especially in Energy and vitality. MERGE trial Wimms et al Lancet Resp Med 2020 PMID 31806413 showed improvements in HrQoL SF36 energy and vitality score in very mild OSA patients.
23. How do data on real-world experience compare with the trial data?	Patients in the trials were sleepier than most patients who are treated with CPAP. We would consider other conditions such as depression, chronic pain or poor sleep hygiene first before suggesting r EDS. It not clear when we would consider calling this idiopathic hypersomnia rather than r EDS.
Equality	

24a. Are there any potential equality issues that should be taken into account when considering this treatment?	Ability of CCGs to pay for treatment. Those areas with high levels of poverty tend to do badly with CPAP and have higher rates of obesity and mental health issues. It is very unlikely that CCGs would take on this additional cost and would be detrimental to the poorest areas.
24b. Consider whether these issues are different from issues with current care and why.	This drug could potentially help these groups most. However they already do poorly on CPAP and are referred late for investigation so having this drug available would not affect that inequality.
Topic-specific questions	
25. What would be the effect on patient compliance with first line therapy such as CPAP if soliramfetol improved OSA symptoms?	Potentially reduce compliance. For some groups it may improve compliance with all treatments if it improves mental health and cognitive problems.
26. What is the ESS level that best reflects 'normal' level of daytime sleepiness, and the group of patients who would most benefit from solriamfetol	I would not be concerned until ESS>14 (this is also used by ATS for their driving regulations). There is some variability of ESS over time and patients with highest ESS tend to improve most. However I would take other quality of life concerns into account. Some patients with low ESS still feel too sleepy and of course symptoms can be confused with fatigue.

treatment?	
27. What would you say is the appropriate definition of treatment response, in terms of ESS reduction or other measurable factors concerned in OSA?	Improvement in ESS of at least 2 points. I would not necessarily expect a normalisation if the patient felt better with increased functioning. It would be worth considering whether carrying out a SF12 or SF6 in clinical practice is useful here? Most sleep physicians are pragmatic however and easily able to tell if a patient feels better but it may help with reimbursement.
28. How is ESS seen to vary over time in patients from this population from the initial consultation, without solriamfetol treatment?	There is variation by a few points over time but I know of no studies looking at this in detail. Generally patients do well on CPAP and those that are sleepy usually have other causes that need to be addressed. We should also ask when does this become idiopathic hypersomnia and should we be carrying out actigraphy in all patients? This group tend to be very sleepy and not vary with time despite CPAP (if OSA is present).

PART 2 – Technical engagement questions for clinical experts	
Issues arising from technical engagement	
We welcome your response to the questions below, but you do not have to answer every question. If you think an issue that is important to clinicians or patients has been missed in the ERG report, please also advise on this in the space provided at the end of this section. The text boxes will expand as you type. Your responses to the following issues will be considered by the committee and may be summarised and presented in slides at the appraisal committee meeting. For information: the professional organisation that nominated you has been sent a technical engagement response form (a separate document) which asks for comments on each of the key issues that have been raised in the ERG report, these will also be considered by the committee.	
[insert issue as described in ERG report	
[insert issue as described in ERG report	
[insert issue as described in ERG report	
[insert issue as described in ERG report	

[insert issue as described in ERG report	
[insert issue as described in ERG report	
Are there any important issues that have been missed in ERG report?	

PART 3 -Key messages

16. In up to 5 sentences, please summarise the key messages of your statement:

- This is a novel drug that could help some groups of patients with residual sleepiness on CPAP therapy especially those who are excessively sleepy due to mental health or cognitive issues.
- It is effective and has few side effects.
- It is not clear how the diagnosis of residual EDS will be defined and investigated nor who will carry out these tests.
- It is likely to increase the workload of specialist centres as smaller centres may not have the resources to carry out these tests.
- It is also likely that extra resource would be required to monitor CPAP more effectively and to prescribe the drug based on these observations.

Thank you for your time.

Please log in to your NICE Docs account to upload your completed document, declaration of interest form and consent form.

……

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NICE National Institute for Health and Care Excellence

Clinical expert statement & technical engagement response form

Solriamfetol for treating excessive daytime sleepiness caused by obstructive sleep apnoea

Thank you for agreeing to comment on the ERG report for this appraisal, and for providing 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. The ERG report and stakeholder 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.

Information on completing this form:

- In **part 1** we are asking you to complete questions where we ask for your views on this technology. You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.
- In **part 2** we are asking you to give your views on key issues in the Evidence Review Group (ERG) report that are likely to be discussed by the committee. An overview of the key issues are summarised in the executive summary at the beginning of the ERG report.
- The key issues in the ERG report reflect the areas where there is uncertainty in the evidence, and because of this the cost effectiveness of the treatment is also uncertain. In part 2 of this form we have included any of the issues raised by the ERG where we think having a clinical perspective could help either:
- resolve any uncertainty that has been identified
  OR
- provide missing or additional information that could help committee reach a collaborative decision in the face of uncertainty that cannot be resolved.

In **part 3** we are asking you to provide 5 summary sentences on the main points contained in this document.

Please return this form by **5pm** on **[insert deadline for comments]**

Completing this form

Part 1 can be completed anytime. We advise that the final draft of part 2 is completed after the expert engagement teleconference (if you are attending/have attended). This teleconference will briefly summarise the key issues, any specific questions we would like you to answer and the type of information the committee would find useful.

Important 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 want to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Do not include medical information about yourself or another person that could identify you or the other person.
- 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.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.

PART 1 – Treating a patient with excessive daytime sleepiness caused by obstructive sleep apnoea and current treatment options	
About you	
1. Your name	**ARI MANUEL**
2. Name of organisation	**LIVERPOOL UNIVERSITY FOUNDATION TRUST**
3. Job title or position	**CONSULTANT IN SLEEP AND VENTILATION**
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 excessive daytime sleepiness caused by obstructive sleep apnoea? ☐ a specialist in the clinical evidence base for excessive daytime sleepiness caused by obstructive sleep apnoea 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.)	☐ yes
7. Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	**Nil**
The aim of treatment for excessive daytime sleepiness caused by obstructive sleep apnoea	
8. What is the main aim of treatment? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability.)	Reduce EDS in patients with OSA already on maximal therapy (CPAP or JAD eg) who do not have another cause of EDS eg medication or other medical condition. Not for PRIMARY OSA treatment. Also this abnormal levels of sleepiness not just people who are just sleepy I think there is a lack of knowledge in terms of effect of blood pressure, long term – and I therefore think we should need to see what happens. Risk profile is less than modafinil (but will likely less effective)
9. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm,	Reduction in ESS of 2 Patient related outcome measure which reflects improvement in EDS. EDS is the most limiting symptom – but not easy to monitor or follow

or a reduction in disease activity by a certain amount.)	
10. In your view, is there an unmet need for patients and healthcare professionals in excessive daytime sleepiness caused by obstructive sleep apnoea?	OSA services in the UK are over stretched with diagnosis and treatment of OSA with CPAP (especially post-COVID-19) There is a significant proportion of patients who remain with EDS despite maximal NHS available therapy (in the most cases CPAP therapy) which the patient is currently compliant. There is very little/no option for this group of patients currently. The is a complex journey for the patient at the moment. There is also a shortage of sleep specialists. The partner to the patient is often affected. The main issue
What is the expected place of the technology in current practice?	
11. How is the condition currently treated in the NHS?	No treated, or modafinil in rare cases. Some are labelled with secondary sleep diagnosis – Idiopathic hypersomnolence (perhaps incorrectly)
• Are any clinical guidelines used in the treatment of the condition, and if so, which?	No. Clinical guidelines is to investigate EDS in patients on CPAP, but practice varies around the UK. No treatments limit investigation pathways
• 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.)	No clear pathway in the UK. Likely large variation based on exposure of cases eg bigger centres with access to advanced testing eg PSG/MSLT who treat patients with sleep conditions eg Narcolepsy may be different to other centres No pathway in US European (France) may have pathways; potentially liked to payments based on performance (payment dependent on compliance with CPAP)

• What impact would the technology have on the current pathway of care?	Would need a total change in the pathway as patients with EDS would need to be followed up and also those already on CPAP would also need to be captured
12. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	
• How does healthcare resource use differ between the technology and current care?	There is no treatment in this area currently used (perhaps the combination of CPAP with JAD or modafinil but this is rare)
• In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	Secondary care specialist clinics (ie those which have the ability to perform the more advance testing for EDS on CPAP as well those which are use to titration of medication in sleep disorders) Potential for shared care with primary care
• What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	Will need more sleep labs with the capability to perform tests to assess – eg MSLT/actigraphy More physiologists to perform and interpret tests potentially More physical sleep labs to performs tests More training (to primary and secondary care) to identify patients on CPAP with residual EDS
13. Do you expect the technology to provide clinically meaningful	Yes – there is no current care in this area

benefits compared with current care?	
• Do you expect the technology to increase length of life more than current care?	There has to be a tangible link between improving EDS and life expectance – I am not sure of the evidence base in that area
• Do you expect the technology to increase health-related quality of life more than current care?	Yes – EDS is the primary compliant for patient with OSA – could have a profound benefit
14. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	Yes – patients newly established on CPAP vs patients who have been on CPAP
The use of the technology	
15. 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	More difficult – as mentioned earlier these patients may not be followed up currently (potential unmet need) – there is likely a need for more staff, training, equipment and physical space

treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed.)	
16. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	Informally – likely failure to work (i.e. no improvement with EDS) or significant side effects
17. 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?	Unclear but likely some benefits with reduced hospital admission or visits to primary care or potential use of medications such as sedatives, anti-depressants and opiate based drugs
18. 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	Yes – no current treatment in this area so could have subsequential benefit (which needs to be offset with the substantial infrastructure improvement needed)

improve the way that current need is met?	
• Is the technology a 'step-change' in the management of the condition?	Yes
• Does the use of the technology address any particular unmet need of the patient population?	Yes – as noted above
19. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	Depends on side-effect – need to consider CVS SE but this needs to be considered in the increased activity of patients when EDS improves
Sources of evidence	
20. Do the clinical trials on the technology reflect current UK clinical practice?	
• If not, how could the results be extrapolated to the UK setting?	The tests used are not freely available in the UK but data can be extrapolated

	All patients recruited in trials are moderate and severe and there was no increase in withdrawal in CPAP use. Withdrawal study shows return of EDS
• What, in your view, are the most important outcomes, and were they measured in the trials?	Improvements in ESS
• If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?	
• Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	No
21. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	No
22. Are you aware of any new evidence for the comparator treatment(s) since the publication	No

of NICE technology appraisal guidance TA139?	
23. How do data on real-world experience compare with the trial data?	Limited real world data
Equality	
24a. Are there any potential equality issues that should be taken into account when considering this treatment?	Need to ensure
24b. Consider whether these issues are different from issues with current care and why.	Not different from current care
Topic-specific questions	
25. What would be the effect on patient compliance with first line therapy such as CPAP if	Patients who were already non compliant – remain non compliant Those who were compliant – likely remain compliant although some would potential reduce CPAP usage

soliramfetol improved OSA symptoms?	
26. What is the ESS level that best reflects 'normal' level of daytime sleepiness, and the group of patients who would most benefit from solriamfetol treatment?	Normal Below 9-10 (I guess the range would be 9-12; dependant on age sex social class ethnicity) Likely 12 – 20 range (anyone over 20 may not have EDS just from OSA)
27. What would you say is the appropriate definition of treatment response, in terms of ESS reduction or other measurable factors concerned in OSA?	ESS – 2 OR PROMS regarding sleepiness
28. How is ESS seen to vary over time in patients from this population from the initial consultation, without solriamfetol treatment?	Massive individual variation (between people or within the same individual over a short time frame) Influence by age, gender, social class, ethnicity Very unclear if EDS increases over time in a clinical population (maybe some anthropology evidence)

PART 2 – Technical engagement questions for clinical experts	
Issues arising from technical engagement	
We welcome your response to the questions below, but you do not have to answer every question. If you think an issue that is important to clinicians or patients has been missed in the ERG report, please also advise on this in the space provided at the end of this section. The text boxes will expand as you type. Your responses to the following issues will be considered by the committee and may be summarised and presented in slides at the appraisal committee meeting. For information: the professional organisation that nominated you has been sent a technical engagement response form (a separate document) which asks for comments on each of the key issues that have been raised in the ERG report, these will also be considered by the committee.	
[insert issue as described in ERG report	
[insert issue as described in ERG report	
[insert issue as described in ERG report	
[insert issue as described in ERG report	

[insert issue as described in ERG report	
[insert issue as described in ERG report	
Are there any important issues that have been missed in ERG report?	

PART 3 -Key messages

16. In up to 5 sentences, please summarise the key messages of your statement:

-
-
-
-
-

Thank you for your time.

Please log in to your NICE Docs account to upload your completed document, declaration of interest form and consent form.

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NICE National Institute for Health and Care Excellence

Technical engagement response form

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

As a stakeholder you have been invited to comment on the ERG report for this appraisal. The ERG 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 key issues below. You do not have to provide a response to every issue. 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 included in the committee papers in full and may also be summarised and presented in slides at the appraisal committee meeting.

Deadline for comments **5pm on Friday 5 February 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 ERG report which summarises the background and submitted evidence, and presents the ERG's summary of key issues, critique of the evidence and exploratory analyses. This will provide context and describe the questions below in greater detail.
- Please ensure your response clearly identifies the issue numbers that have been used in the executive summary of the ERG report. If you would like to comment on issues in the ERG report that have not been identified as key issues, you can do so in the 'Additional issues' section.
- If you are the company involved in this appraisal, please complete the 'Summary of changes to the company's cost-effectiveness estimates(s)' section if your response includes changes to your cost-effectiveness evidence.
- 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)	Stakeholder Bioprojet (previously Lincoln Medical)
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	None

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Key issues for engagement

Please use the table below to respond to questions raised in the ERG report on key issues. You may also provide additional comments on the key issue that you would like to raise but which do not address the specific questions.

Key issue	Does this response contain new evidence, data or analyses?	Response
Key issue 1: Potential reduction in patient compliance with primary OSA therapy during concomitant solriamfetol treatment **[report section 3.2.6.1.4]**	NO	In general, we believe that the use of intention to treat (ITT) populations in clinical trial analyses tend to ensure that adherence issues are incorporated into the primary results of any clinical trials and economic modelling derived from those trials.
Key issue 2: Model population **[report section 4.2.3]**	NO	In line with our response above, as a general principle we believe that the population modelled should reflect the clinical trial population, insofar as is possible. We therefore believe that the Epworth Sleepiness Scale (ESS)≥10 threshold is the appropriate one to use
Key issue 3: Definition of treatment response **[report section 4.2.6.3]**	NO	No comments
Key issue 4: Adjustment of ESS for the placebo effect ('centring') **[report section 4.2.6.2]**	NO	Clearly this issue is fundamental to the results of the economic analysis. The ERG has addressed this robustly in their scenario analyses and we have no further comments to make.
Key issue 5: Health utility values **[report section 4.2.7]**	NO	In-study EQ-5D measurements generally appear to be a poor determinant of health state utilities in people with excessive daytime sleepiness (EDS). This was recognised and reflected in the mapping approach used in NICE TA139 (Continuous positive airway pressure for the treatment of obstructive sleep

		apnoea/hypopnoea syndrome) and is supported by expert opinion and the literature[1-3]. EQ-5D and other quality of life (QOL) measures were not specifically designed to assess aspects of QOL in patients with obstructive sleep apnoea (OSA) or EDS and sleep is not included as a specific dimension. We therefore support the company's use of ESS to utility mapping.
Key issue 6: Partner utilities **[report section 4.2.7.4]**	NO	No comments
Key issue 7: Treatment discontinuation and loss of response rates **[report section 4.2.6.4]**	NO	No comments
Key issue 8: The impact of adverse events (AE) **[report section 4.2.8.3.2]**	NO	Whilst minor side effects are generally a minor contributor to the incremental cost-effectiveness ratio (ICER), in this instance we agree that AEs resulting in hospitalisation should be included, as they incur a significant cost.
Key issue 9: Solriamfetol dose split **[report section 4.2.8.1.2]**	NO	No comments, as the relevant data are redacted.

Additional issues

Please use the table below to respond to additional issues in the ERG report that have not been identified as key issues. Please do **not** use this table to repeat issues or comments that have been raised at an earlier point in this appraisal (e.g. at the clarification stage).

Issue from the ERG report	Relevant section(s) and/or page(s)	Does this response contain new evidence, data or analyses?	Response
Additional issue 1: Primary versus Secondary Care prescribing	Not mentioned by the ERG	NO	The company submission states that solriamfetol is not associated with any significant ongoing monitoring requirements. On this basis, one would expect that prescribing would occur in Primary Care, in line with other drug therapies used in OSA. Indeed, market research undertaken by Bioprojet with 20 UK hospital consultants suggests that oral wake-promoting products for EDS, such as pitolisant and solriamfetol, although initiated in Secondary Care, would be prescribed in the Primary Care setting on an 'amber' shared care protocol basis. This aligns with the prescribing patterns for many hospital-initiated products for long-term chronic conditions. The Summary of Product Characteristics for the product states that treatment should be initiated by a clinician with expertise in the field, but there is no requirement for ongoing hospital supervision. However, in the current BNF (https://bnf.nice.org.uk/medicinal-forms/solriamfetol.html), the product is listed as "hospital use only".

			This issue needs to be reviewed, as if there is indeed a requirement for hospital monitoring, this needs to be identified and costed within the economic model. If not, the reason for the product being considered "hospital use only" should be addressed.

References

1. Telephone conversation: Tricia Dixon (JB Medical) and John O'Reilly (Consultant Physician in Respiratory and Sleep Medicine) 17 September 2019. 2019
2. CRD/CHE Technology Assessment Group University of York. The Continuous Positive Airway Pressure for the treatment of obstructive sleep apnoea-hypopnoea syndrome: a systematic review and economic analysis, 2007.
3. Moyer CA, Sonnad SS, Garetz SL, Helman JI, Chervin RD. Quality of life in obstructive sleep apnea: A systematic review of the literature. *Sleep Medicine* 2001; **2**(6): 477-91.

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

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

Evidence Review Group's summary and critique of the company's response to technical engagement

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Commercial in confidence (CIC) information in blue

Academic in confidence (AIC) information in yellow

LIST OF ABBREVIATIONS

AE	Adverse event
AIC	Academic in confidence
AHI	Apnoea Hypopnoea Index
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
CS	Company submission
CSR	Clinical study report
DSU	Decision Support Unit
EDS	Excessive daytime sleepiness
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
HRG	Healthcare Resource Group
HRQoL	Health-related quality of life
ICER	Incremental cost-effectiveness ratio
IPD	Individual patient level data
ITT	Intent to treat
KOL	Key opinion leader
LOCF	Last observation carried forward
	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
PSS	Personal Social Services
QALY	Quality-adjusted life year
QoL	Quality of life
RCT	Randomised controlled trial
RTM	Regression to the mean
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
SmPC	Summary of product characteristics
TA139	NICE TA139 CPAP for the treatment of OSAHS
TA	Technology appraisal
TE	Technical engagement
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

1. Introduction

This document is the Evidence Review Group's (ERG) summary and critique of the response by the company, Jazz Pharmaceuticals, to the key issues for technical engagement (TE) proposed in the ERG report for this appraisal (post-factual accuracy check version). The ERG received the company's response on Monday 8th February 2021.

The company's TE response form contains the following information:

- A written response to each of the 9 key issues, most of which include additional evidence and/or analyses, to varying degrees (see Table 1).
- A set of updated cost-effectiveness results, incorporating the company's preferred base case following technical engagement. This is accompanied by the results of sensitivity analyses, threshold analyses, scenario analyses and subgroup analyses.
- All cost-effectiveness estimates are based on a proposed confidential patient access scheme (PAS) discount price.

In this report we present the following:

- Our critique of the company's response to each of the 9 issues for technical engagement (Section 2).
- A validation of the results of the company's updated cost-effectiveness analysis, and the results of updated ERG scenario analyses (Section 3).

Table 1 Summary of key issues for technical engagement

Issue number	Summary of issue	Does this response contain new evidence, data or analyses?
1	Potential reduction in patient compliance with primary OSA therapy during concomitant solriamfetol treatment [ERG report section 3.2.6.1.4]	Yes – additional evidence
2	Model population [ERG report section 4.2.3]	Yes – updated company analyses
3	Definition of treatment response [ERG report section 4.2.6.3]	Yes – additional evidence
4	Adjustment for the placebo effect ('centring') [ERG report section 4.2.6.2]	Yes – additional evidence
7	Treatment discontinuation and loss of response rates [ERG report section 4.2.6.4][a]	Yes – updated company analyses
5	Health utility values [ERG report section 4.2.7]	Yes – updated company analyses
6	Partner utilities [ERG report section 4.2.7.4]	No
8	The impact of adverse events [ERG report section 4.2.8.3.2]	Yes – additional evidence
9	Solriamfetol dose split [ERG report section 4.2.8.1.2]	Yes – additional evidence

[a] Issues 4 and 7 are closely related and for this reason we have re-ordered the sequence of issues in this report so that issue 7 is discussed consecutively to issue 4.

2. Critique of the company's response to key issues for technical engagement

2.1 Issue 1 – Potential reduction in patient compliance with primary OSA therapy during concomitant solriamfetol treatment [ERG report section 3.2.6.1.4]

Summary of key issue

It is suggested that compliance with primary OSA therapy may be compromised by a reduction in daytime sleepiness when talking solriamfetol. If patients attribute the improvement in their symptoms to solriamfetol they may not necessarily maintain their level of compliance to primary OSA therapy. This is plausible given the simplicity of solriamfetol administration (a once daily tablet) versus the more complex administration of PAP devices or maintenance of lifestyle changes. The company submission (CS) reported that there was no meaningful change in use of primary OSA therapy devices (an exploratory outcome measure) between baseline and week 9-12 in the pivotal phase III TONES 3 trial. However, this analysis did not distinguish between compliance/non-compliance to primary OSA therapy at the start of the trial. Thus, it is not clear whether patients classified as compliant with primary OSA therapy would reduce or maintain compliance when taking solriamfetol. The ERG considers that further information is needed to overcome the limitations in the design and reporting of these analyses.

What additional evidence or analyses might help to resolve this key issue?

The ERG recommended greater clarity and transparency in the reporting of these exploratory compliance analyses:

- Clarification of the relevant analysis populations in TONES 3 and TONES 5 for this outcome
- Sensitivity analysis to assess the impact of missing data
- Sub-group analysis stratified by compliance at baseline

Supporting evidence may also be useful if available:

- The likelihood of compliance issues over the longer term e.g. was this seen in users of modafinil in the real-world setting?
- What effect a drop in CPAP compliance has on ESS (and other outcomes e.g. AHI, snoring, cardiovascular risk)

Further expert clinical advice would be informative on:

- How compliance is measured in practice and the likely impact on patient outcomes if it is compromised.
- How clinicians would react if primary OSA therapy compliance worsened after initiation of solriamfetol.

Summary of company's response	ERG comments
• The company summarises a recently published peer-reviewed manuscript (Schweitzer et al 2020)[1] assessing compliance with primary OSA therapy with long-term solriamfetol use. These data are from the TONES 5 study - an open-label study of the safety and tolerability of solriamfetol (75, 150 or 300 mg) for up to 52 weeks.	• The ERG notes that the data reported in the manuscript appear to be reported in various parts of the company submission (CS) and the TONES 5 clinical study report (CSR). Thus, the manuscript summarises previously available data on compliance, as opposed to introducing additional data. • Of two cohorts enrolled in the TONES 5 study, the cohort of most relevance to this appraisal is Group A, which comprises a sample of patients who were enrolled directly from the pivotal phase III TONES 3 trial (N=333). • The manuscript provides estimates of primary OSA therapy device compliance up to week 40 of open-label treatment (Table 2 of the manuscript). • The ERG notes that these estimates are not reported separately for patients classified as compliant or non-compliant at baseline, as we had recommended. • These data combine patients on different solriamfetol doses and appear to include some taking the unlicensed 300mg dose.
	Key results • At baseline 235 of 333 (70.6%) patients reported using a primary OSA therapy, the majority of whom used PAP (222). • For participants using an airway therapy, mean device use at baseline was 90% of nights, 6.6 hours/night, and use ≥50%/night on 90% of nights. Changes from baseline to week 40 in these three measures of compliance were minimal (0.9%, -0.8 hours, and 6.5%, respectively). • The manuscript states that "the level of primary OSA therapy use remained acceptable based on current standards with no meaningful changes over 40 weeks of solriamfetol treatment".

	Risk of bias due to missing data • The ERG notes that the baseline number of hours per night and baseline use on ≥50%/night measures were reported for sub-samples of patients with electronically retrievable data (n=147) and patients with diary data (n= 89), respectively. Furthermore, change from baseline values for all three measures were based on sub-samples of patients for whom complete (paired) data were available at each follow-up timepoint. At some timepoints the magnitude of missing data was substantial. • The handling of these missing data is not described in the manuscript. Table 14.2.5.1a of the TONES 5 CSR states that the last observation carried forward imputation method was used, but it also says that only subjects with non-missing OSA diary data were summarised, inferring that there was no imputation for diary data at least (applicable to just over a third of the sample). • The ERG assumes that missing data is due to a combination of patients who discontinued the study, patients no longer using primary OSA and patients who continued the study but had missing compliance data. • Overall, missing data remains a source of potential bias because it could be from patients less likely to comply with primary OSA therapy. • The ERG suggests caution in the interpretation of these analyses due to the magnitude of missing data and ambiguities about how these were accounted for in the analysis.
	Questionable generalisability to clinical practice • Given the fact that patients enrolled in Group A of TONES 5 had completed the 12-week TONES 3 parent study it could be suggested that they may be more inclined to use primary OSA therapy consistently. The

	results of TONES 5 therefore may not be fully applicable to the general OSA patient population. • The ERG also notes that mean baseline levels of compliance appear relatively high (e.g. mean use of primary airway OSA therapy was 90% of nights), which may reflect a clinical trial sample, rather than a typical patient population. • Having said that, one of the clinical experts to the ERG commented that they would only consider prescribing solriamfetol to patients who demonstrated good compliance to primary OSA therapy. If other clinicians follow a similar approach then the TONES 5 study population could be considered generalisable to current practice. Further expert clinical advice would be informative.
ERG conclusion • The ERG's concerns about the exploratory primary OSA therapy compliance analysis remain. • The Schweitzer et al 2020[1] manuscript summarises data previously available in the CS and TONES 5 CSR. The results indicate little meaningful change in primary OSA therapy during solriamfetol treatment. Whilst the results are informative, they should be interpreted with caution, primarily due to the risk of bias from substantial missing data and ambiguity about how these missing data were analysed. • The findings may not necessarily be generalisable to a typical patient population seen in practice. Further expert clinical opinion would be informative.	

2.2 Issue 2 – Model population [ERG report section 4.2.3]

Summary of key issue

The mean baseline ESS score ([redacted]) in the company's base case model is increased by the use of individual patient data (IPD) for people with ESS>10 (rather than ESS≥10 as in the TONES 3 trial population). The company argues that ESS=10 falls within the range considered 'normal' in UK clinical practice (CS Table 6 and page 118). This assumption also increases the estimated proportion of responders over the 12-week induction treatment period.

We believe that the entry requirement for the TONES 3 trial (i.e. ESS ≥10) would be more appropriate. Restriction to a population with ESS>10 is likely to enhance the effectiveness, and hence cost-effectiveness of solriamfetol. However, this also increases uncertainty by reducing the sample size on which the analysis is based.

What additional evidence or analyses might help to resolve this key issue?

Expert opinion on the ESS level that best reflects a 'normal' level of daytime sleepiness, and the group of patients who would most benefit from solriamfetol treatment.

Company response	ERG comments
• The company's position on the appropriate patient population for solriamfetol has changed: their modelled population is now patients with baseline ESS > 12 (previously it was baseline ESS >10). • Their decision is based on evidence from the NHWS Survey showing a substantial improvement in QoL demonstrated at ESS scores >12.	• We note that the size of the IPD set used in this updated analysis is substantially reduced from that of the original analysis reported in CS. In the updated analysis, the standard care arm comprises [redacted] patients, the solriamfetol 37.5 mg, 75 mg and 150 mg arms comprise [redacted], [redacted] and [redacted] patients, respectively. The respective reductions in the proportion of patients in the standard care arm and solriamfetol arms are [redacted]%, [redacted]%, [redacted]% and [redacted]%. • The company's updated patient population conflicts with the company's statement regarding prescribing patterns from a US survey, according to which, [redacted]. This may indicate that the population in the TONES 3 trial is not

• They argue that this group represents patients with the greatest clinical need. • The company also cite the results of their interviews with key opinion leaders (KOLs) in which opinions on the definition of normal EDS varied.	representative of the patient population in US clinical practice.
• The company's decision problem is now restricted to patients with more severe EDS (i.e. ESS > 12).	• The ERG's updated cost-effectiveness analysis is based on the revised modelled patient population (i.e. ESS > 12) (section 3 below).
ERG conclusion • Restricting the modelled population to patients with more severe EDS (ESS > 12) is likely to improve the cost effectiveness of solriamfetol, but with increased uncertainty due to the reduced patient sample size. • Further expert clinical advice on identifying patients with the greatest clinical need for solriamfetol would be informative.	

2.3 Issue 3 – Definition of treatment response [ERG report section 4.2.6.3]

Summary of key issue

There is considerable variation in the definition of treatment response in clinical practice. Clinical advice to the ERG is that clinicians would also consider other factors in addition to EDS (ESS) when assessing treatment effectiveness. In the company's base case, response is defined as at least a 3-point reduction in ESS from baseline to 12 weeks. Alternative definitions of response (reductions in ESS score of 2 or 4 or more points) are assessed in scenario analyses.

The economic model assumes that treatment would be discontinued at 12 weeks if the response is judged inadequate. A less stringent definition of response is likely to reduce the average effectiveness and cost-effectiveness of continued solriamfetol treatment.

What additional evidence or analyses might help to resolve this key issue?
Clinical advice on an appropriate definition of treatment response, in terms of ESS score reduction or other measurable factors.

Company response	ERG comments
• The company acknowledges variability in the use of the ESS in clinical practice, and that there is no officially recognised definition of response based on absolute reduction in ESS. • Clinicians may accept variable levels of ESS improvement, and/or any patient reported improvement in condition as meaningful, based on KOL interviews. • KOL interviews suggest that the patient's self-reported improvement in their condition, and/or a reduction of 2–4 points in ESS reflects a clinically meaningful response to treatment.	• The ERG believes that an ESS score reduction of 2 points is a more appropriate definition of treatment response. • This estimate is in-keeping with the findings of the company's KOL interviews. The ERG notes that [redacted]. It also reflects expert clinical advice to the ERG.
• The company suggests the proposed minimally important clinical difference (MCID) of 2-3 points proposed by Patel et al (2018 [2] is "overly stringent" when applied to patients with a baseline ESS of 14 or greater. The company therefore chose not to base their estimate of treatment response on the Patel MCID.	• The ESS score reduction of 2 points reported by Patel et al. 2018 accords with expert clinical opinion, as described above.
• The company retains their base case estimate of treatment response as an ESS score reduction of at least **3 points.**	• The ERG retains their base case estimate of treatment response as an ESS score reduction of at least **2 points**. • We explore other estimates in scenario analyses (see section 3 below).

ERG conclusion

- No change made to the company or the ERG's base case. Further expert clinical perspectives may be informative.

2.4 Issue 4 – Adjustment for the placebo effect ('centring') [ERG report section 4.2.6.2]

Summary of key issue

In the TONES 3 trial, reductions in mean ESS scores were observed for patients in the solriamfetol and placebo arms. The company use a 'centring' approach to adjust the TONES 3 IPD used in the economic model by removing the placebo arm effect from both study arms. This is appropriate if the placebo arm improvement was caused by observation of patients in the clinical trial that would not have occurred in routine practice (a 'Hawthorne' effect). However, it would not be appropriate if the placebo effect was caused by a natural 'regression to the mean' (RTM), as this would still have occurred outside the clinical trial.

The company provides a good discussion of potential causes for the ESS placebo effect in support of their centring approach (CS B.3.3.2). In particular, we note their argument that a placebo effect was not observed in TONES 3 for the Maintenance of Wakefulness Test (MWT), which tends to support the argument that the ESS placebo effect was not caused by regression to the mean. We note, however, that the MWT and ESS do measure different (though related) things, and it is possible that MWT is more stable over time, mitigating against a regression to the mean effect, whereas the ESS as a self-reported measure is more susceptible to natural variation, and hence to regression to the mean.

There is no direct evidence for the cause of the ESS placebo effect or the appropriateness of adjustment to remove it from the economic analysis.

What additional evidence or analyses might help to resolve this key issue?

- Observational evidence on the degree of natural variation in ESS over time for people with EDS caused by OSA that has not been satisfactorily treated with established clinical management.
- Expert advice on how ESS is seen to vary over time in patients from this population from the initial consultation, without solriamfetol treatment.

Company response	ERG comments
• The company retains the 'Hawthorne' assumption in their base case model, assuming that observation of patients in the trial context improves outcomes for both active and placebo arms, but that these effects would not occur in routine practice. • The TONES 3 ESS data in the model is therefore adjusted to remove the mean placebo effect for standard care and solriamfetol ('centring'). • The company also argue that there is evidence to support the more extreme 'true placebo' scenario, with the assumption of no ESS improvement under standard care alone, but the full trial response for solriamfetol treatment.	• The ERG takes the position that standard practice is to model trial data 'as is', rather than to adjust for placebo effects. RTM is a real possibility for an outcome subject to random error, which "needs to be ruled out as a cause of an observed change before any other explanation is sought." [3] • Consideration of RTM is particularly important for the economic analysis because the model uses raw individual patient data (IPD), with no adjustment for baseline ESS (unlike the main clinical analyses for TONES 3, which used a mixed model with a baseline covariate). • For our preferred analysis, we adapted the company's model to remove their placebo adjustment and added a fourth health state to allow for ESS improvement with standard care alone (see Key Issue 7 below for discussion of the ERG non-centred 4-state version of the company's model). • The ERG version of the model is consistent with an RTM interpretation of the trial placebo effect. It may also be appropriate if interaction with healthcare practitioners has a psychological benefit or provokes lifestyle change or better compliance with standard care.[4]

• The company present evidence from their clinical trial programme to examine potential causes of the placebo effect (sections 1.3.1 and 1.4, of the TE response). • They argue that this evidence conflicts with an assumption of RTM and supports a 'true placebo' interpretation.	• See Appendix below for a full ERG commentary on evidence in the company's TE response. • There were mean improvements in ESS and MWT in the whole TONES 3 placebo group, which were sustained over 12 weeks. The 12-week ESS reduction was larger for patients with a high baseline value. • The TONES 4 randomised withdrawal study and randomised withdrawal phase of the TONES 5 open label solriamfetol treatment study showed a mean improvement in ESS over two weeks for blinded placebo. The company has not presented information about within or between patient variation in these studies. • It is difficult to interpret results from the analyses the company presents in response to TE (which link data from the TONES 3 and TONES 4 trials to the TONES 5 study) because the methods of analysis are not explained or justified. We also note that the analyses for patients who progressed to open label solriamfetol from the TONES 3 and 4 trials (company TE response Figures 1 and 7) are susceptible to selection bias, as the patients who progressed may not be fully representative of a typical patient population.
The company argue that measuring variation in ESS would occur in a real world setting is difficult, as it would be difficult to rule out whether a change was due to a change in treatment or lifestyle.	• There are clearly costs and practical challenges to collection of cohort data. However, we suggest that it may not be necessary to adjust for changes in lifestyle or compliance with elements of standard treatment, as these may reflect the natural variation within standard care.

The company presents 'real world' evidence from a small qualitative study (n=15) on change in ESS between screening and baseline (mean interval of 4.3 days).	• The sample size and duration of follow-up in the qualitative study are too low to provide representative information about the population of interest.
The company has submitted a summary of advice from KOLs interviewed after consideration of the ERG report	• We note that the KOL interviews report cites some conflicting views on the reproducibility of the ESS, and comments that suggest ESS can vary over time for individuals. The ERG also highlights the clinical expert statement to NICE from Dr Manuel in this regard.
ERG conclusion • The ERG does not consider that the company has provided sufficient evidence to rule out RTM as (at least) a contributory factor to the observed placebo response. • We therefore think that the model without adjustment for placebo effects should provide the starting point for economic analysis. • Analyses with placebo adjustment to explore Hawthorne or 'true placebo' explanations are useful scenarios that the appraisal committee may want to consider.	

2.5 Issue 7 - Treatment discontinuation and loss of response rates [ERG report section 4.2.6.4]

Summary of key issue

The company report that solriamfetol treatment discontinuation due to treatment emergent adverse events (TEAEs) and loss of response in the TONES 3 and 5 trials was dose dependent. However, the modelled rates in the company base case are the same across all solriamfetol doses.

Loss of response with standard care is not an issue for the company model, with 'centring' assumptions, because ESS is assumed to be constant without solriamfetol. However, in our version of the model, we assume that ESS can vary with standard care and hence response is possible without solriamfetol. The subsequent change in ESS and loss of response over time with standard care is highly uncertain because we do not have follow up for this group beyond 12 weeks.

What additional evidence or analyses might help to resolve this key issue?
Observational data on how ESS changes over time with standard care, as suggested above to investigate the placebo effect and appropriateness of centring, would also help to address the question of the loss of response rate with standard care.

Company response	ERG comments
• Revised company base case includes dose-specific estimates of discontinuation due to loss of efficacy and adverse events for solriamfetol.	• We agree with this approach, as adopted in the ERG preferred analysis.
• The company model does not include discontinuation in the standard of care without solriamfetol arm, as these patients were assumed not to receive an active treatment and thus cannot discontinue 'nothing'. • Despite the assumption of regression to the mean, the ERG model allows patients on standard care to discontinue treatment ('nothing') and in those patients who discontinued, their ESS score was able to deteriorate and in doing so, to move away from the implied "true mean".	• We did not apply a 'discontinuation rate' to the standard care arm in the company's 3-state model (see formulae in discontinuation_rates!E12-H12 and _Engine_OSA!J12, in the ERG model). • In the ERG 4-state model we assume that patients on standard care alone can have an initial 'response' (i.e. reduction in ESS), consistent with that in the TONES 3 placebo arm, but we assume that this response can be lost over time. We believe that this is a reasonable approach. • An alternative 4-state model structure could have also included 'recurrence of response' for both standard care and solriamfetol arms: with transitions from the non-responder (NR) health state to the responder no treatment (RNT) state. This may fit better with our assumption that ESS can sometimes improve for patients treated with standard care alone. However, it would have complicated the model but with limited impact on the results, as 'recovery of response' would apply to standard care and solriamfetol treatment arms.
• The company argues that it might be expected that the	• In our base case, we set the loss of response parameter for standard care equal to the observed

loss of response rate would be higher for patients on standard care only than for those with add-on solriamfetol.	rate of discontinuation from solriamfetol due to loss of efficacy from the TONES 3 trial (weighted mean across doses): [redacted] in year 1 and [redacted] per year subsequently. • Uncertainty over within-patient variation in ESS over time with standard care has not been resolved. On reflection, we agree that it is reasonable to assume that the loss of response rate is likely to be higher with standard care alone than with solriamfetol. We have therefore conducted an additional scenario analysis to illustrate the effect of a higher loss of response rate for standard care (see section 3 below). • Note that we do not, and have not, argued that reducing the standard care loss of response parameter to zero would be plausible.
• It is unclear what specific adjustments were made to the Markov trace formulae by the ERG.	• Changes to the company's model are highlighted in green in the ERG version of the model. For the 3-state Markov trace formulae, see columns: I to K in the model engine sheets (_Engine_OSA and _Engine_OSA_PSA). • We note however, that this change has a negligible impact in the company's 3-state model.
ERG conclusion • We consider that the ERG 4-state version of the model, without adjustment for the placebo effect, is an appropriate starting point for the economic analysis. • There is uncertainty over the rate at which patients on standard care with an initial ESS improvement, might be expected to lose this response over time. • We present additional scenario analysis to investigate the effect of assuming a higher loss of response rate under standard care.	

2.6 Issue 5 – Health utility values [ERG report section 4.2.7]

Summary of key issue

EQ-5D-5L results from the TONES 3 trial did not show consistent trends over time or evidence of treatment effects for solriamfetol. The company argues that this is due to the high baseline EQ-5D utilities in the TONES 3 population, and they question the sensitivity of the EQ-5D for detecting the Health-Related Quality of Life (HRQoL) effects of OSA. The other generic HRQoL measure in the trial (the SF-36) did show some evidence of a treatment effect for solriamfetol, although this was inconsistent between doses.

There is some evidence from the literature that utility measures that include an energy or vitality dimension, such as the SF-6D or AQOL, are better at predicting overall HRQoL. However, we note that the company has not presented SF-6D results for TONES 3.
The company use a 'mapping' approach to estimate EQ-5D utility as a function of ESS in their base case economic analysis. A new mapping equation was estimated from data collected from an online sample of people with self-reported OSA. The NHWS mapping study was described in detail and it appeared to be well-conducted. Other sources of utility estimates used in the model are the ESS to EQ-5D mapping study by McDaid et al. that was used in the NICE appraisal of CPAP for OSA (TA139); and a new time trade off (TTO) study.

What additional evidence or analyses might help to resolve this key issue?

- SF-6D results for TONES 3 would help to clarify the direct utility effect of solriamfetol add-on therapy.
- Clarification is needed on whether the valuation method used to calculate index scores for the EQ-5D-5L in TONES 3 and in the NHWS mapping study are consistent with the NICE reference case.

Company response	ERG comments
The company reiterates arguments in favour of the NHWS mapping study rather than using direct trial data as the source of utility estimates in the model.	• See ERG report section 4.2.7.5 for a summary of the relative merits of alternative sources of utility (EQ-5D-5L from TONES 3, McDaid mapping, NHWS mapping and TTO). • The company has not responded to the ERG's request for SF-6D results from TONES 3. We believe this could have provided important direct information about the utility impact of solriamfetol

	treatment, [redacted] [redacted] (CS Table 14), and evidence that the SF-6D has greater sensitivity than the EQ-5D in OSA studies and, more generally, that utility instruments that include a vitality or energy dimension (including the SF-6D) are better at predicting HRQoL measured with visual analogue scale (see ERG report section 4.2.7.2). • We also note that the company have not commented on ERG's criticisms of the NHWS dataset or TTO approach.
The NHWS utility mapping in the company's original base case analysis, used country-specific utility values for individuals. The mapping has been updated to use the UK value set for all survey participants.[5] This updated mapping has been used in the revised company base case analysis. The company also state that the NHWS mapping study was completed in line with NICE DSU guidelines.	• The revision to the NHWS mapping is appropriate, to comply with the NICE reference case requirements. • It is also reassuring that the mapping complies with NICE DSU guidance. • The revised NHWS mapping results are reported in the Kantar study report.[5] The final coefficients are reported in Table 7 of the Kantar report: mean utility reduction per unit increase in ESS of [redacted] for ESS score 0-11 and [redacted] for ESS score 12-24. These slopes are higher than in the original analysis ([redacted] and [redacted] respectively). Consequently, it is expected that the revised NHWS coefficients yield a higher estimated QALY gain for solriamfetol than the company's original base case analysis. • We note that there are some differences in the NHWS mapping coefficients from the Kantar report and those cited in the table of model parameters in the company's TE response document. This appears to be due to rounding, although the signs of the coefficients for Female and BMI are reversed. The company did not submit an updated economic model, so we cannot check what

	estimates they used in their revised base case results. However, we confirm that these differences have a negligible impact on the cost-effectiveness results.

ERG conclusion

- We welcome the revision to the NHWS mapping equation for utilities used in the company's base case analysis. This uses UK valuations for the van Hout 'crosswalk' EQ-5D-5L utility estimates for all participants in the NHWS survey, which is appropriate.
- However, we are disappointed that the company has not responded to our request for SF-6D utility results from the TONES 3 trial data. This could have provided additional direct information about the utility impact of solriamfetol treatment, which we believe is important, given uncertainty over the applicability of the mapped utility estimates.

2.7 Issue 6 – Partner utilities [ERG report section 4.2.7.4]

Summary of key issue

The NICE reference case specifies that economic evaluations should include "all direct health effects, whether for patients or, when relevant, carers". Partners of people with OSA are not necessarily carers, although some would be. However, paragraph 5.1.7 of the NICE methods guide states that the perspective on outcomes should include "all direct health effects, whether for patients or for other people". It is therefore unclear whether partner utilities should be included in the assessment of cost-effectiveness of solriamfetol.

The company's TTO study estimated utility associated with health states describing OSA and four levels of EDS severity from the perspective of patients and of their partners. The study is described in detail and appears to have followed recommended methods. However, the ERG questions whether the TTO utility estimates are comparable with utilities obtained from the EQ-5D, which NICE prefers.

What additional evidence or analyses might help to resolve this key issue?

- Clarification of precedent for NICE appraisals on the inclusion of partner utilities in health economic evaluations.
- Evidence of the magnitude of utility loss associated with living with a partner who has OSA and EDS, derived according to NICE reference case methods.

Company response	ERG comments
• The company refers to the scenario presented in their submission which includes partner utilities. They state that this is more likely to reflect the true impact of solriamfetol on the HRQoL of patients and partners than the base case (which does not include partner utilities).	• We agree that it is appropriate for the company to have attempted to quantify the health impact of EDS on carer/partner utility in a scenario for consideration alongside the base case.
• The company argue that there is a substantial disutility to the partner of a patient with EDS, due to impacts on marital and family relationships, social life and finances.	• We understand that EDS is associated with such effects, which can impact on the well-being of carers, partners and family members. • There is a question of whether all these impacts represent 'health' effects, and if not, whether they fall within the NICE reference case.
• The relationship between patient and partner utility in the company's scenario is estimated using results from the TTO study. The company reiterate that "it was not possible to test the relationship in EQ-5D of a partner related to a patient's ESS".	• We reiterate concerns about the high uncertainty over the TTO estimates of the relationship between patient and partner utilities (ERG report section 4.2.7.4).
ERG conclusion • The company has not provided any additional information with regard to this issue and no changes have been made to the cost effectiveness analysis. • Clarification from the appraisal committee regarding whether or not partner utilities should be included as a health effect for solriamfetol, is welcome.	

2.8 Issue 8 - The impact of adverse events [ERG report section 4.2.8.3.2]

Summary of key issue

The company's model does not include any disutility or treatment cost for TEAEs not leading to discontinuation. This was based on the observation that most AEs in TONES 3 were transient and mild/moderate in severity. For adverse events that led to treatment

discontinuation, the model includes the cost of one general practitioner consultation. We note that a proportion of serious adverse events (SAEs) in the 150 mg arm of TONES 5 led to hospitalisation [redacted].

What additional evidence or analyses might help to resolve this key issue?

The ERG included a cost for SAEs that led to hospitalisation in the ERG base case.

Company response	ERG comments
• The company analyses English Hospital Episodes Statistics, which describes the current management of the reported AEs. • They argue against inclusion of stroke in the ERG model as it already occurs in the target population in the existing clinical landscape without solriamfetol.	• In the ERG analysis, hospitalisation costs were estimated based on the rates of SAE-related hospital admission of patients with OSA in TONES 5 that were considered related to solriamfetol. • Among 144 patients titrated to 150 mg per day, [redacted]) were hospitalized due to SAEs (see ERG report Table 40). The company states, however, that hospitalisation of only [redacted] (who had a cerebrovascular accident), was drug related. The company argues that resource use related to TEAEs in the ERG analysis was overestimated, because we costed hospital admissions in line with the hospitalisations reported in the TONES 5 trial. • We acknowledge that the hospitalisation cost is a proxy for TEAEs. We believe, however, that the estimate included in our base case is conservative. • A recent study by Patel et al.[6] reports that the average cost to the NHS and PSS of managing stroke in the first year is £18,081 (in GBP 2014-15 prices), with the cost in subsequent years of £7,759 per person per year. • We note the impact of the TEAEs on HRQoL is not modelled. This would increase the ICER if included.
• No change to model assumptions	• In our updated base case we retain the cost of hospitalisation (see section 3 below). (NB. This cost has a relatively small impact on the company's base-case ICER, increasing it by less that £1,000).

ERG conclusion

- The ERG considers it appropriate to include hospitalisation costs for SAEs in patients taking solriamfetol.

2.9 Issue 9 - Solriamfetol dose split [ERG report section 4.2.8.1.2]

Summary of key issue

The proportion of people who would be prescribed the 37.5 mg, 75 mg and 150 mg doses of solriamfetol in clinical practice is uncertain. This obviously impacts on the estimated cost of solriamfetol, but it also affects the overall estimates of response and ESS change, and the rates of discontinuation.

The company states that "US data suggests a [redacted] dose split for the 37.5 mg, 75 mg and 150 mg doses, respectively" (CS page 169). However, they suggest that UK prescribers will be more conservative compared with those in the US and they therefore assume a split of 40/40/20 in their base case. This may be a reasonable assumption, although one of our clinical advisors suggested that some clinicians may start patients on the 75 mg dose to reduce the time and resource needed for dose titration. The company argues that the dose split in the TONES 5 open-label follow up study is not informative for clinical practice, because participating clinicians were advised to increase to the maximum dose subject to tolerance.

What additional evidence or analyses might help to resolve this key issue?

Additional utilisation data from other countries with similar prescribing behaviour may help to inform the estimated use of solriamfetol 37.5 mg, 75 mg and 150 mg doses in the UK.

Company response	ERG comments
• Cites KOL experience of dose titration for narcolepsy as basis for the assumption in treatment of OSA of starting at the lowest dose and slowly titrating upwards (a "cautious approach").	• Expert clinical advice to the ERG is that starting with the lowest dose may not always be considered. • Clinical expert advice in relation to the appraisal of solriamfetol as a treatment for narcolepsy is that the treatment would usually be escalated to the maximum dose regardless of side effects.

• The company rejects the US source estimation of dose split in favour of anticipated UK prescribing practice. • They make no mention of investigating prescribing behaviour in other countries.	• Evidence on prescribing practice in other countries, where available, would be informative.
• The company retains the 40/40/20 dose split in their base case.	• In the ERG analyses we retain the split of [redacted] for the 37.7 mg, 75 mg and 150 mg solriamfetol doses, respectively, as informed by US data. We regard this as a conservative assumption. • We also conduct scenarios to estimate the impact of uncertainty around the dose split, as reported in section 3 below.
ERG conclusion • In the absence of prescribing evidence or further expert opinion the ERG considers it appropriate to retain the [redacted] dose split in the base case.	

3. Updated cost-effectiveness results - ERG summary and critique

3.1 Company's revised base case cost-effectiveness results

Table 2 presents the company's base case (with ERG corrections) ICER, in addition to ICERs generated by application of a series of ERG scenarios. The ERG scenario which omits the company's centring adjustment and included the ERG's four-state model (Key issues 4 and 7) has the greatest impact on the results, with an ICER of [redacted] per QALY gained. The next most influential scenario is the model time horizon: the ICER for the time horizon of 1 year is [redacted].

Table 2 Company base case (ERG corrected) and ERG scenario analyses: PAS price

Individual scenarios on the base case	Treat-ment	Costs	QALYs	Incr. costs (£)	Incr. QALYs	ICER (£/QALY)
Company base case (with ERG corrections)	SC	£0	10.033			
	SOL	[redacted]	10.412	[redacted]	0.379	[redacted]
No centring + 4-state model	SC	£0	10.516			
	SOL	[redacted]	10.716	[redacted]	0.199	[redacted]
Timepoint of response assessment: 8 weeks	SC	£0	10.033			
	SOL	[redacted]	10.412	[redacted]	0.379	[redacted]
Treatment response: reduction in ESS≥2	SC	£0	10.033			
	SOL	[redacted]	10.441	[redacted]	0.408	[redacted]
Treatment response: reduction in ESS≥4	SC	£0	10.033			
	SOL	[redacted]	10.356	[redacted]	0.324	[redacted]
Cost of hospitalisation due to SAEs	SC	£0	10.033			
	SOL	[redacted]	10.412	[redacted]	0.379	[redacted]
[redacted] SOL dose split	SC	£0	10.033			
	SOL	[redacted]	10.442	[redacted]	0.409	[redacted]
20/40/40 SOL dose split	SC	£0	10.033			
	SOL	[redacted]	10.494	[redacted]	0.461	[redacted]
Model time horizon: 1 year	SC	£0	0.275			
	SOL	[redacted]	0.292	[redacted]	0.017	[redacted]
Model time horizon: 5 years	SC	£0	2.286			
	SOL	[redacted]	2.415	[redacted]	0.128	[redacted]
Compliant patients	SC	£0	9.939			
	SOL	[redacted]	10.280	[redacted]	0.341	[redacted]
Non-compliant patients	SC	£0	10.181			
	SOL	[redacted]	10.636	[redacted]	0.454	[redacted]
50%/50% split (compliant/ non-compliant)	SC	£0	10.060			
	SOL	[redacted]	10.458	[redacted]	0.398	[redacted]

Incr: incremental; SC: standard care; SOL: solriamfetol combination

3.2 ERG's revised preferred assumptions

The ERG base-case assumptions are listed below:

- Model population: patients with ESS > 12 at baseline (Key issue 2)
- The use of 4-state model without centring of the IPD (Key issues 4 and 7)
- Hospitalisation costs for SAEs as used in the ERG report (Key issue 8)
- The use of updated NHWS mapping coefficients based on the UK value set (Key issue 5)

3.3 Cost-effectiveness results based on the ERG's base case

Table 3 reports the cumulative change in the ICER leading to the ERG's base case, which represents the combined effect of all ERG assumptions which differ from those in the company's base case. The most significant increase in the ICER is caused by switching to the 4-state model structure and removing the centring adjustment of the IPD (Key issues 4 and 7).

Table 3 ERG cumulative analysis and base-case results for population with ESS > 12 at baseline: PAS price

Cumulative analyses	Treat-ment	Costs	QALYs	Incr. costs (£)	Incr. QALYs	ICER (£/QALY)
Company base case (with ERG corrections)	SC	£0	10.033			
	SOL	[redacted]	10.412	[redacted]	0.379	[redacted]
Treatment response: reduction in ESS≥2	SC	£0	10.033			
	SOL	[redacted]	10.441	[redacted]	0.408	[redacted]
SOL dose split: [redacted]	SC	£0	10.033			
	SOL	[redacted]	10.474	[redacted]	0.441	[redacted]
Hospitalisation costs	SC	£0	10.033			
	SOL	[redacted]	10.474	[redacted]	0.441	[redacted]
Removing centring and switching to 4-state model	SC	£0	10.638			
	SOL	[redacted]	10.810	[redacted]	0.171	[redacted]
ERG base case	SC	£0	10.638			
	SOL	[redacted]	10.810	[redacted]	0.171	[redacted]

Incr: incremental; SC: standard care; SOL: solriamfetol combination

3.4 Scenario analyses conducted on the ERG's revised preferred assumptions

The results of scenario analyses conducted on the ERG base case are presented in Table 4 below. Reverting to the three-state model structure and inclusion of the centring adjustment of the IPD (as in the company's analysis) produces the most significant reduction in the ICER (Key issues 4 and 7). The assumption of 1-year time horizon increases the ICER.

Table 4 ERG scenario analyses: PAS price

Individual scenarios on the base case	Treat-ment	Costs	QALYs	Incr. costs (£)	Incr. QALYs	ICER (£/QALY)
ERG base case	SC	£0	10.638			
	SOL	[redacted]	10.810	[redacted]	0.171	[redacted]
With centring and 3-state model	SC	£0	10.033			
	SOL	[redacted]	10.474	[redacted]	0.441	[redacted]
Timepoint of response assessment: 8 weeks	SC	£0	10.639			
	SOL	[redacted]	10.810	[redacted]	0.171	[redacted]
Treatment response: reduction in ESS≥3	SC	£0	10.525			
	SOL	[redacted]	10.745	[redacted]	0.220	[redacted]
Treatment response: reduction in ESS≥4	SC	£0	10.469			
	SOL	[redacted]	10.698	[redacted]	0.229	[redacted]
Without the cost of hospitalisation due to SAEs	SC	£0	10.638			
	SOL	[redacted]	10.810	[redacted]	0.171	[redacted]
40/40/20 SOL dose split (company base case)	SC	£0	10.627			
	SOL	[redacted]	10.785	[redacted]	0.158	[redacted]
20/40/40 SOL dose split	SC	£0	10.675			
	SOL	[redacted]	10.897	[redacted]	0.222	[redacted]
Time horizon: 1 year	SC	£0	0.300			
	SOL	[redacted]	0.308	[redacted]	0.007	[redacted]
Time horizon: 5 years	SC	£0	2.475			
	SOL	[redacted]	2.528	[redacted]	0.053	[redacted]
Compliant patients	SC	£0	10.482			
	SOL	[redacted]	10.627	[redacted]	0.145	[redacted]
Non-compliant patients	SC	£0	10.911			
	SOL	[redacted]	11.155	[redacted]	0.244	[redacted]
ICER for 50%/50% split (compliant/non-compliant)	SC	£0	10.697			
	SOL	[redacted]	10.891	[redacted]	0.194	[redacted]
Loss of response in SC arm (1.5 x base-case values)[1]	SC	£0	10.541			
	SOL	[redacted]	10.810	[redacted]	0.268	[redacted]
	SC	£0	10.465			

Individual scenarios on the base case	Treat-ment	Costs	QALYs	Incr. costs (£)	Incr. QALYs	ICER (£/QALY)
Loss of response in SC arm (2 x base-case values)[1]	SOL	[redacted]	10.810	[redacted]	0.344	[redacted]

SC: standard care; SOL: solriamfetol combination.
[1] The base-case values for the first and subsequent years were estimated as weighted averages of the treatment discontinuation rates due to loss of response in the solriamfetol arms (37.5 mg, 75 mg and 150 mg).

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4. Appendix - ERG commentary on empirical evidence on the placebo effect (Key issue 4)

4.1 Mean changes in ESS and MWT from TONES 3 (company's TE response Figures 2 and 3)

- Mean changes in ESS for the TONES 3 placebo arm indicate an improvement in week one that is sustained up to the endpoint of 12 weeks.
- The more objective MWT measure shows a similar pattern, but with a clear dose response relationship for solriamfetol. This outcome is not used in the model.
- At a group level, the trial outcomes do not show evidence of waning of the placebo effect over the 12-week trial period.

4.2 Relationship between ESS baseline and mean change from TONES 3 (company's TE response Figure 5)

- The company state that quantification using the methodology suggested by Barnett 2005 gives a regression to the mean of 0.497 points. Further information is required to understand the validity and meaning of this statistic. For example, the method in the Barnett paper is for normally distributed data whereas ESS scores as well as change in ESS from baseline are skewed.
- Figure 5 is unnecessarily complicated, which obscures the interpretation. E.g. the rationale for separating compliant and non-compliant subgroups is not given, and this dilutes the power of the analysis. Similarly, stratifying by low, mild and severe ESS is unnecessary and potentially misleading; as all trial participants (with the possible exception of those with a baseline ESS of 10) have a higher than normal level of daytime sleepiness at baseline (trial entry criterion is ESS≥10).
- The outcome of interest is change from baseline to week 12 (response assessment), with placebo treatment. This shows a negative trend for 12-week change in ESS by baseline ESS.
- We illustrate this with a simple scatterplot of individual patient data from the economic model (***[redacted]*** *1* below). This shows that the reduction from baseline ESS is larger for patients who started with a high baseline value (indicated with a polynomial trend line).

[redacted] 1

Source: Produced from individual patient data in the company's economic model

4.3 Mean change in ESS between TONES 3/4 and TONES 5 data (company's TE response Figure 1 and 7)

- No information is provided about the number of patients included in these analyses, or whether they are representative of the whole trial population. It is possible that there is a selection effect, as patients who progress to TONES 5 may differ from those who do not.
- The footnote to Figure 1 states that there is a break of unknown duration between the end of TONES 4 and entry to TONES 5. The reason for this is unclear (are there not dates for these events in the trial databases?). It also seems to conflict with the inclusion of TONES 4 patients in the combined GLM time series analysis (see section below).

4.4 Repeated measures analysis of TONES 3, 4 & 5 data (company's TE response Figure 4)

- This analysis is poorly reported.
    - No information is given about the sample in this analysis. We cannot therefore assess whether it is susceptible to selection bias (patients in TONES 3 or 4, who did not progress to 5).

    - How is time allocated for the transition from TONES 4 to 5? The footnote to Figure 1 says that this duration is unknown.
    - There is no explanation or justification for how the covariates were chosen.
- It is also difficult to know how to interpret the results, given the complexity of the graph.

4.5 Screening and baseline measurements from TONES 3, 4 & 5 (company's TE response Table 1)

- The sample sizes (n=[redacted], n=[redacted]) are very low, and it is unclear how these patients were selected or if they are representative of the trial populations.

4.6 Real world evidence: qualitative burden of illness study

- Very small sample (n=[redacted]) with screening and baseline measurements of ESS taken within a short time interval (mean gap [redacted]days).
- No methods are reported for sample selection, so it is not clear if these patients are representative.