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

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

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

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

Single Technology Appraisal

Response to consultee, commentator and public comments on the Appraisal Consultation Document (ACD)

Type of stakeholder:

Consultees – Organisations that accept an invitation to participate in the appraisal including the companies, national professional organisations, national patient organisations, the Department of Health and Social Care and the Welsh Government and relevant NHS organisations in England. Consultees can make a submission and participate in the consultation on the appraisal consultation document (ACD; if produced). All non-company consultees can nominate clinical experts and/or patient experts to verbally present their personal views to the Appraisal Committee. Company consultees can also nominate clinical experts. Representatives from NHS England and clinical commissioning groups invited to participate in the appraisal may also attend the Appraisal Committee as NHS commissioning experts. All consultees have the opportunity to consider an appeal against the final recommendations, or report any factual errors, within the final appraisal document (FAD).

Clinical and patient experts and NHS commissioning experts – The Chair of the Appraisal Committee and the NICE project team select clinical experts and patient experts from nominations by consultees and commentators. They attend the Appraisal Committee meeting as individuals to answer questions to help clarify issues about the submitted evidence and to provide their views and experiences of the technology and/or condition. Before they attend the meeting, all experts must either submit a written statement (using a template) or indicate they agree with the submission made by their nominating organisation..

Commentators – Commentators can participate in the consultation on the ACD (if produced), but NICE does not ask them to make any submission for the appraisal. Non-company commentator organisations can nominate clinical experts and patient experts to verbally present their personal views to the Appraisal Committee. Commentator organisations representing relevant comparator technology companies can also nominate clinical experts. These organisations receive the FAD and have opportunity to report any factual errors. These organisations include comparator technology companies, Healthcare Improvement Scotland any relevant National Collaborating Centre (a group commissioned by NICE to develop clinical guidelines), other related research groups where appropriate (for example, the Medical Research Council and National Cancer Research Institute); other groups such as the NHS Confederation, the NHS Commercial Medicines Unit, the Scottish Medicines Consortium, the Medicines and Healthcare Products Regulatory Agency, the Department of Health and Social Care, Social Services and Public Safety for Northern Ireland).

Public – Members of the public have the opportunity to comment on the ACD when it is posted on the Institute's web site 5 days after it is sent to consultees and commentators. These comments are usually presented to the appraisal committee in full, but NICE reserves the right to summarise and edit comments received during consultations, or not to publish them at all, where in the reasonable opinion of NICE, the comments are voluminous, publication would be unlawful or publication would be otherwise inappropriate.

Please note: Comments received in the course of consultations carried out by NICE 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 submissions that NICE has received, and are not endorsed by NICE, its officers or advisory committees.

<table>
<tr><th>Comment number</th><th>Type of stakeholder</th><th>Organisation name</th><th>Stakeholder comment
Please insert each new comment in a new row</th><th>NICE Response
Please respond to each comment</th></tr>
<tr><td>1</td><td>Consultee</td><td>Jazz Pharmaceuticals</td><td>
Comment 1. On the request for clinical and cost effectiveness analysis of solriamfetol alone compared with standard care

In the ACD, the Committee recalled that the marketing authorisation for solriamfetol includes people who may not be using a primary OSA therapy anymore. The Committee asked the Company to provide clinical and cost-effectiveness of solriamfetol alone for people who cannot tolerate CPAP. The Company believes this would include the subgroup of people with mental health or neurodegenerative conditions who may be unable to adequately use CPAP regularly (described by the clinical expert in ACD 3.17) (3).
Analysis of the TONES 3 IPD determined that 26.5% of patients in the solriamfetol arm and 30.3% of patients in the placebo arm were not using a primary OSA therapy at baseline. The remaining 73.5% and 69.7% of patients, respectively, were using a primary OSA therapy. Of the patients using a primary OSA therapy, approximately 92% were using PAP, approximately 2% were using non PAP, and in 6%, the device was not specified. This is consistent with UK clinical practice where the majority of people using a primary OSA therapy will be receiving CPAP therapy (8). As could be expected in clinical practice, patients were using this primary OSA therapy at varying degrees of compliance, however all patients were encouraged to continue a stable level of use/non use of their primary OSA therapy throughout the study. The IPD for TONES 3 can therefore be categorised into (i) patients who were using a primary OSA therapy at baseline vs (ii) patients who were not using a primary OSA therapy at baseline. Note that patients in group may have been using diet and lifestyle modifications however this data was not captured in the trial therefore these data can be considered a proxy for ‘solriamfetol alone for people who cannot tolerate CPAP’. Summary data for patients in TONES 3 using vs not using primary OSA therapy is presented in Table 3. While this was not a pre-specified analysis in the original study, it is of merit here to provide the necessary evidence for translation of the clinical trial data into a real-world context.

Table 1. Scenario analysis: summary data for patients using vs not using primary OSA therapy at baseline in TONES 3
<table>
<tr><th></th><th>Responders (%)</th><th>Mean change in ESS from baseline</th><th>Responders (%)</th><th>Mean change in ESS from baseline</th></tr>
<tr><th></th><th colspan="2">Using primary OSA therapy</th><th colspan="2">Not using primary OSA therapy</th></tr>
<tr><td>Solriamfetol 37.5 mg</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td></tr>
<tr><td>Solriamfetol 75 mg</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td></tr>
<tr><td>Solriamfetol 150 mg</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td></tr>
</table>
Abbreviations: ESS, Epworth Sleepiness Scale; OSA, obstructive sleep apnoea
</td><td>Comment noted. The committee considered the analysis provided by the company and ERG for people not using primary obstructive sleep apnoea therapy at baseline. The FAD has been updated to reflect this – See FAD section 3.6 for information on the analysis of solriamfetol with and without standard care.</td></tr>
</table>

<table>
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<tr><td></td><td></td><td></td><td>
The results of cost effectiveness analyses for these subgroups of patients are presented in Table 4 and Table 5. This analysis demonstrates that solriamfetol is a cost-effective treatment choice both in patients who are receiving a primary OSA therapy and those who are not using a primary OSA therapy (for example due to CPAP intolerance, neurodegenerative conditions, or mental health conditions as described in the ACD), with both ICERs falling substantially below the acceptable £20,000 per QALY gained specified by the Committee.

Table 2. Scenario analysis: patients using a primary OSA therapy at baseline
<table>
<tr><th>Technologies</th><th>Total costs (£)</th><th>Total QALYs</th><th>Total LYG</th><th>Incremental costs (£)</th><th>Incremental QALYs</th><th>ICER versus baseline (£/QALY)</th></tr>
<tr><td>Standard of care without solriamfetol</td><td>£4,811</td><td>11.575</td><td>30.215</td><td></td><td></td><td></td></tr>
<tr><td>Standard of care with the addition of solriamfetol ([redacted] 37.5, 75, 150 mg)</td><td>[redacted]</td><td>11.991</td><td>30.215</td><td>[redacted]</td><td>0.415</td><td>[redacted]</td></tr>
</table>
Abbreviations: ICER, incremental cost effectiveness ratio; LYG, life years gained; QALYs, quality adjusted life years.

Table 3. Scenario analysis: patients not using a primary OSA therapy at baseline
<table>
<tr><th>Technologies</th><th>Total costs (£)</th><th>Total QALYs</th><th>Total LYG</th><th>Incremental costs (£)</th><th>Incremental QALYs</th><th>ICER versus baseline (£/QALY)</th></tr>
<tr><td>Standard of care without solriamfetol</td><td>£4,810</td><td>11.373</td><td>30.207</td><td></td><td></td><td></td></tr>
<tr><td>Standard of care with the addition of solriamfetol ([redacted] 37.5, 75, 150 mg)</td><td>[redacted]</td><td>11.893</td><td>30.207</td><td>[redacted]</td><td>0.521</td><td>[redacted]</td></tr>
</table>
Abbreviations: ICER, incremental cost effectiveness ratio; LYG, life years gained; QALYs, quality adjusted life years.
</td><td></td></tr>
<tr><td>2.</td><td>Consultee</td><td>Jazz Pharmaceuticals</td><td>Comment 2. On the request for sensitivity analyses to assess the impact of missing data on adherence to primary therapy at baseline

Per ACD 3.6, the committee concluded that compliance to a primary OSA therapy like continuous positive airway pressure (CPAP) is unlikely to be affected by treatment with solriamfetol, but that more data were needed.</td><td>Comment noted. The committee considered the company's</td></tr>
</table>

Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
			The Company previously presented the peer-reviewed Schweitzer 2021 manuscript that examined whether or not solriamfetol affected compliance to using primary OSA therapy (i.e. positive airway pressure [PAP], oral pressure therapy, an oral appliance, or an upper airway stimulator) in an open-label extension trial (9). These data have, therefore, been assessed by the clinical and academic sleep community and published as a valuable information resource to understand the impact of introducing solriamfetol on primary OSA therapy compliance, including PAP or CPAP compliance. Although this is a peer-reviewed manuscript, the ERG raised queries about the analyses: • ACD 3.6 "The ERG noted that the results of these analyses were highly uncertain because of missing data and poor reporting. It said that the estimates were not reported separately for people classified as 'compliant' (adherent) or 'non-compliant' at baseline" (3). • ERG Report Section 3.2.6.1.4 and ERG critique of company response to TE, Section 2.1 raise queries around the impact of missing data and the definition of compliant in the Schweitzer 2021 analysis (9). The Company provide detailed information in Sections 0 and 0 to clarify that the populations used in the compliant/non-compliant analyses in Schweitzer 2021 were based on compliance levels as defined at baseline, and to address the issue of potential missing data. In addition, the Company present a new analysis using a "worst-case scenario" approach in Section 0, which demonstrates that even in the worst-case scenario, compliance to primary OSA therapy is maintained at high levels. In conclusion, the data demonstrate that patients' use and compliance to primary OSA therapy is unlikely to be affected by the introduction of solriamfetol for managing their residual EDS. **2.1. Definition of compliance/non-compliance in Schweitzer 2021** The Company clarify that the analysis is stratified by compliance levels to primary OSA therapy *at baseline.* The definition of compliance was as per the primary studies that formed the basis for the Schweitzer 2021 analysis; this same definition was used as a stratification factor in the stratified randomisation in order to minimise the potential bias described by the ERG. The definition of "compliant" vs "non-compliant" was described in the methods by Schweitzer 2021: • "For the purpose of defining subgroups of participants who were adherent or nonadherent to OSA primary therapy at baseline, adherence was defined as device use for at least 4 hours per night on at least 70% of nights for devices with downloadable data; device use on at least 70% of nights for devices with no downloadable data; or effective surgical intervention" (9). The definition in the primary studies (i.e. TONES 3) was: • "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), [redacted] use of an oral appliance on ≥70% of nights (≥5 of 7 nights/week), or receipt of an effective surgical intervention for OSA symptoms". **2.2. Query over missing data in Schweitzer 2021** Within the Schweitzer 2021 publication, missing data were accounted for in a standardised way (last observation carried forward); this is acknowledged in the paper as a minor limitation of the analysis (9). Furthermore, the Schweitzer 2021 publication states:	analysis on adherence to primary OSA therapy. It concluded that adherence to primary OSA therapy is unlikely to be affected by treatment with solriamfetol. The FAD has been updated to reflect this – see FAD section 3.5 for information on adherence to primary OSA therapy.

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			• "OSA therapy use data were summarised by percentage of nights used (from electronically retrievable and diary data), number of hours/night for those with electronically retrievable information, and percentage of nights used more than half of the night for those who completed a diary." Note that the d**ata** from the analysis considered as "missing" by the ERG were only considered missing due to a difference in the way that "compliance" was determined in patients using a primary OSA therapy that *did* versus *did not* collect compliance data electronically. Patients reporting use of a device for which usage data could not be retrieved electronically reported their usage and estimated the duration of use as (i) half of the night, (ii) less than half of the night or (iii) don't know. This was a pre-specified measure of compliance, and this electronic compliance data is not considered to be missing data. **2.3. New analysis demonstrating that data acknowledged as missing in Schweitzer 2021 have minimal impact on rates of compliance to primary OSA therapy** In addition to the substantial certainty on primary OSA therapy compliance provided in the published Schweitzer 2021 manuscript, the Company have since conducted additional sensitivity analyses to assess the impact of the small amount of missing data. Applying the most austere imputation methodology based on the CHMP Guideline on Missing Data in Confirmatory Clinical Trials (10), the Company re-evaluated the data using a worst case analysis of missing data. A model was created where missingness[1] of data was assumed "not at random", and entirely dependent on random allocation to treatment or control arms, consistent with a worst-case scenario described by CHMP (10). Although this scenario is implausible due to the stratified randomisation of compliance, it helps to illustrate what an extreme scenario could cause in terms of primary OSA therapy compliance: • The observed cohort had [redacted] patients with [redacted] observations. After adjustment for three baseline factors (hours of PAP use per night, percentage of nights compliant, and ESS), data were imputed as non-compliant for missing patients in the solriamfetol arm and compliant for the placebo arm. This resulted in [redacted] patients with [redacted] observations. • In this austere model, participants compliant to primary OSA therapy at baseline and subsequently receiving solriamfetol demonstrated [redacted] hours by week 12. Compliance with PAP is generally defined as ≥4 hours on 70% of nights (11-14), and this level of compliance remains reassuringly exceeded in this pessimistic 'worst case scenario' analysis. **2.4. Conclusion regarding concerns over missing data and definition of compliance with primary OSA therapy** In conclusion, primary OSA therapy use is unlikely to be affected by the introduction of solriamfetol. The clinical expert opinion presented in ID1065 for pitolisant agrees with the clinical expert advice collected by Jazz and presented in ID1499 for solriamfetol, that it is unlikely that pharmacotherapy will result in a reduction in compliance to primary OSA therapy (1,	

[1] Missingness can be defined as (i) the existence of missing data and (ii) the mechanism that explains the reason for the data being missing. The extent to which missing values lead to biased conclusions about the magnitude of any treatment effect is influenced by many factors, including the relationship between missingness, treatment assignment and outcome; the type of measure employed to quantify the treatment effect and the expected changes over time for the variables being measured.

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			3). It follows that as solriamfetol is unlikely to displace primary therapies such as CPAP for OSA, there is no onward impact on partner utilities removing the uncertainty around this topic (ACD 3.12 “The impact on partner utilities of displacing treatments such as CPAP was also uncertain.”). Furthermore, the data in the Schweitzer peer-reviewed manuscript and the additional analysis presented here substantially exceed the depth of data presented in ID1065 for pitolisant, where based on patient and clinical expert opinion, the Committee concluded that "CPAP use is unlikely to be affected by treatment with pitolisant hydrochloride because of regular monitoring” (1).	
3.	Consultee	Jazz Pharmaceuticals	**Comment 3. On the request to assess the potential impact of regression to the mean** The Committee would have preferred some analysis assuming a regression to the mean effect. The Company has made some amendments to the model assumptions to facilitate an investigation of the impact of regression to the mean on the ICER. The Company position is that the placebo effect observed in TONES 3 is a true placebo effect, however the Company’s revised model maintains the conservative approach that the placebo effect is due to a Hawthorne effect. Thus any ICERs presented likely underestimate the cost-effectiveness of solriamfetol. **3.1. Context for this analysis** The information supporting the Company’s placebo adjustment using the Hawthorne effect requires an understanding of the TONES clinical trial study designs and the different elements potentially contributing to the placebo effect. A brief summary of these is provided below: 1. TONES 3 was the pivotal randomised controlled trial for solriamfetol in treating EDS due to OSA. Patients were randomised 1:1:1:2:2 to placebo or solriamfetol 37.5, 75, 150, or (unlicensed) 300 mg respectively for the 12 week duration of the trial. 2. All patients enrolled in TONES 3 were receiving standard of care (SoC) to manage their underlying OSA. Patients fell into one of three groups: a. Currently using a primary OSA therapy (including positive airway pressure [PAP], oral pressure therapy, an oral appliance, or upper airway stimulator) b. Historically made an attempt for at least 1 month to use one or more primary OSA therapies with at least 1 documented adjustment to optimise the primary OSA therapy c. Had a history of a surgical intervention intended to treat OSA symptoms 3. Patients continued to use a primary OSA therapy throughout TONES 3, therefore the placebo and solriamfetol arms of the trial, respectively, can be considered to reflect ‘SoC without solriamfetol’ and ‘SoC with the addition of solriamfetol’. This terminology is used throughout this document to describe the arms of the trial as modelled in the CE analysis.	Comment noted. The committee considered the company’s evidence regarding the adjustment for the improvement in the control arm of TONES 3. The FAD has been updated to reflect this – see FAD section 3.8 for information on the mechanisms for adjusting for the improvement in the control arm of TONES 3.

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			4. In TONES 3 patients in the SoC without solriamfetol (i.e. placebo) arm achieved an improvement (i.e. reduction) in mean ESS score from baseline to week 12. Although this improvement did not reach statistical significance, it demonstrated a placebo effect in the trial. 5. Three common placebo elements may be considered in the context of clinical trials (4): a. True placebo effect: psychological patient expectancy that is generalisable to routine practice b. Hawthorne effect: psychological patient expectancy effect that is specific to the clinical trial setting (i.e. a patient's response to observation and assessment) c. Regression to the mean effect: arises from natural variation in the patient's condition over time, and the potential preferential selection of patients with acutely severe disease into trials; these patients are likely to show improvement when disease severity is next measured, regardless of any treatment benefit, as they tend toward their individual mean state. The extent to which the regression to the mean effect occurs in clinical practice depends on the similarities between the criteria used to select patients for treatment in practice vs those used to select patients in the trial. 6. As outlined in the Company submission and per the additional data presented in Section 0 of this document, the ***Company believes the placebo effect observed in TONES 3 was principally due to a true placebo effect.*** However, the ***Company's revised base case analysis conservatively maintains that the improvement in the placebo arm was due to the Hawthorne effect*** (4), such that patients receiving placebo reported a reduction (i.e. improvement) in ESS because they were being observed within the trial. 7. This base-case assumption is consistent with advice from the clinical experts for ID1065 for pitolisant (1), that the placebo effect observed in the pitolisant trials could be Hawthorne effect (i.e. patients reported an improvement in ESS due to more frequent contact with trial investigators than they would have with clinicians in clinical practice). 8. To account for the placebo effect, the Company performed a 'centring exercise' on the TONES 3 individual patient level data to remove the placebo effect from *both* the SoC without solriamfetol (i.e. placebo arm) and the SoC with the addition of solriamfetol groups (i.e. solriamfetol arm) in the model and allow only the incremental effects of solriamfetol to be assessed. This centring exercise was considered plausible by the Committee (3).	

			9. The ERG stated that the improvement in the SoC without solriamfetol arm could, at least in part, be due to a natural 'regression to the mean' effect as described in Point 5 above. The ERG assumed that the response to treatment observed in the placebo group in TONES 3 would also occur in routine clinical practice. To facilitate this assumption, the ERG were required to (ii) modify the model structure and introduce a fourth health-state (Responder No Treatment), and (ii) make a number of assumptions, including: a. the rate at which patients on SoC without solriamfetol discontinue treatment (or move to a non-response state) b. the proportion of patients on solriamfetol who discontinue yet maintain an improvement in their ESS, despite not receiving any treatment 10. In this new 'Responder No Treatment' health state, a proportion of patients who stopped solriamfetol retained an ESS response (despite not receiving active treatment for their EDS). However, this fourth health state and its supporting assumptions in the ERG model led to some implausible results (e.g. in the ERG base case, after a number of years SoC with solriamfetol gains fewer QALYs than SoC without solriamfetol [resulting in the possibility that SoC alone without solriamfetol dominates Soc with the addition of solriamfetol], and that the modelling scenario requires 'no treatment' to be discontinued and thus cannot reflect clinical practice). 11. The Committee was concerned about the validity of some outputs generated by the ERG's model, including the percentage of people in the SoC group who still have a response to treatment at 3 years and 10 years. The Committee noted that the level of response in the SoC group and the difference between the solriamfetol vs placebo groups was implausible. 12. The Committee requested that the Company explore a regression to the mean effect. The Company agrees with the concerns raised by the Committee and therefore the revised Company model retains the original three health state structure. However, the Company has amended other model assumptions to align with the Committee's preferred assumptions and used this revised model to conduct a sensitivity analysis to explore a regression to the mean effect, as requested by the Committee. **3.2. Company model: regression to mean sensitivity analysis** The Committee accepted that there was likely to have been some observation bias in the trial. The Committee acknowledged that there may be some regression to the mean, so there was a need to understand its potential impact by conducting sensitivity analyses (3). As requested by the Committee, the Company model has been amended to allow sensitivity analysis investigating of a potential regression to the mean in TONES 3. This new sensitivity analysis uses the raw unadjusted IPD from TONES 3 for both the SoC without solriamfetol group (i.e. placebo arm of TONES 3) and the SoC with the addition of solriamfetol group (i.e. solriamfetol arm of TONES 3). The original Company model differentiated between responders and non-responders (i.e. those with/without sufficient reduction in ESS, respectively) in both the SoC without solriamfetol arm and SoC with solriamfetol arms. However, in the original model, the centring exercise to adjust for placebo effect meant that all of the patients in the SoC without solriamfetol (i.e. placebo) arm were considered non-responders by default, and therefore those patients remained at their baseline ESS for the lifetime of the model. In order to allow investigation of a regression to the mean, the revised Company model removes the centring exercise and the responder and non-responder dichotomy, and instead considers the SoC without solriamfetol arm as a single group:	

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			• As patients receiving SoC with placebo were not receiving active treatment for their residual EDS, there was no requirement to differentiate between responders and non-responders to treatment (i.e. those with or without an ESS reduction of ≥2 points). The overall mean reduction in ESS for these patients was [redacted] at week 12 of TONES 3, and in this sensitivity analysis, the patients remain at this ESS level for the lifetime of the model. • For patients receiving SoC with the addition of solriamfetol (i.e. receiving active treatment for their residual EDS), the model assesses if patients are responders or non-responders to treatment at week 12 (i.e. those with or without a mean ESS reduction of ≥2 points, per the ERG and Committee's preferred assumption). • In patients receiving SoC with the addition of solriamfetol who do not respond to treatment, and any patients who initially respond but subsequently discontinue due to a lack of efficacy or adverse events (AEs), their ESS upon discontinuing solriamfetol immediately changes to that of the SoC without solriamfetol group ([redacted]), reflecting the (regressed) mean position for a patient now receiving only SoC for their underlying OSA. Table 4 presents results of the sensitivity analysis investigating a regression to the mean effect and allows the relative impact of all three placebo elements (regression to the mean, true placebo and Hawthorne effect) to be explored by providing a weighted average of the three alternative approaches. In this combined placebo effect analysis, the table displays the proportion of the placebo effect contributed by regression to the mean and true placebo, such that the remaining proportion contributed by the Hawthorne effect is calculated as: **% Hawthorne = 100% - (% true placebo + % regression to the mean)** • As outlined in the original Company submission, it **is likely** that the improvement in ESS observed in the SoC without solriamfetol arm is a true placebo effect; in addition, extensive clinical evidence is described in Section 0 of this ACD document further demonstrates the placebo effect in TONES 3 is likely a true placebo and is not regression to the mean. • The Lincoln Medical company submission (Section 2.13.1) for NICE ID1065 for pitolisant (15) notes that a placebo effect is observed in the pitolisant trial; this is also noted in the ACD for ID1065, with the Committee concluding that it would be appropriate to explore approaches to adjust for the placebo effect in the trial (1). The Committee for ID1065 suggested that a centring exercise could be used to adjust for this [i.e. Hawthorne] effect but did not make reference to a regression to the mean effect (1). Based on the above points, the Company maintain their position that the majority of the placebo effect in TONES 3 is a true placebo effect, therefore the ICERs in Table 4 likely underestimate the cost-effectiveness of solriamfetol and the true ICER for solriamfetol is likely in the bottom left hand portion of this table and thus below the acceptable ICER of below £20,000 per QALY gained agreed by the Committee (3). • The top-left ICER reflects the Company's revised base case, with all of the placebo effect due to Hawthorne effect (i.e. 100% Hawthorne effect; calculated as 100% minus [0% true placebo plus 0% regression to the mean]).	

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Conversely, the top-right ICER reflects a highly conservative approach, assuming 33% regression to the mean and 0% true placebo (i.e. 67% Hawthorne effect; calculated as 100% minus [0% true placebo + 33% regression to the mean]).
Table 4. Sensitivity analysis* considering alternative placebo mechanisms (ICERs)
<table>
<tr><th></th><th></th><th colspan="7">Regression to the mean</th></tr>
<tr><th></th><th></th><th>0%</th><th>5%</th><th>10%</th><th>15%</th><th>20%</th><th>30%</th><th>33%</th></tr>
<tr><th rowspan="13">True placebo</th><th>0%</th><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td></tr>
<tr><th>5%</th><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td></tr>
<tr><th>10%</th><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td></tr>
<tr><th>15%</th><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td></tr>
<tr><th>20%</th><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td></tr>
<tr><th>30%</th><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td></tr>
<tr><th>40%</th><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td></tr>
<tr><th>50%</th><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td></tr>
<tr><th>60%</th><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td></tr>
<tr><th>70%</th><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td></td></tr>
<tr><th>80%</th><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td></td><td></td></tr>
<tr><th>90%</th><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td></td><td></td><td></td><td></td></tr>
<tr><th>100%</th><td>[redacted]</td><td></td><td></td><td></td><td></td><td></td><td></td></tr>
</table>
Abbreviations: ICER, incremental cost effectiveness ratio.
*Analysis assumes a dose split of [redacted] for solriamfetol 37.5/75/150 mg.
Grey cells indicate implausible scenarios that exceed the maximum 100%.
</td><td></td></tr>
<tr><td>4.</td><td>Consultee</td><td>Jazz Pharmaceuticals</td><td>Comment 4. On the request to use SF-6D data from the Company's trials to assess quality of life measures

It is recognised that there is considerable need for a well validated and sufficiently responsive quality of life measure for evaluating people with sleep disorders (16). The EQ-5D and SF-6D questionnaires are both generic measures to ascertain health status and neither questionnaire includes a sleep domain nor a dimension to specifically capture the impact of EDS on quality of life in people with OSA.</td><td>Comment noted. The committee recognised that mapping should be considered a</td></tr>
</table>

Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
			The committee wanted to see the SF-6D in the analysis and concluded that mapping from the ESS to the EQ-5D may not adequately capture changes in quality of life. However, neither the EQ-5D nor the SF-36 data collected in the TONES trials reflected the substantial burden of OSA on QoL. Despite the high burden of illness in patients with such a disabling symptom, the baseline utility scores collected in the trials were inconsistent with the widely accepted negative impact of EDS and OSA. The reasons why these health questionnaires were incapable of capturing changes in QoL in the trials are discussed at length in the Company submission Form B and Technical Engagement response (e.g. a lack of a sleep domain, inability to capture impact on relationships, high baseline utility scores, patient adaptation to sleepiness over time). Furthermore, as acknowledged by the ERG, the 12-week trial duration was likely insufficient to capture the effect of solriamfetol treatment on quality of life. Whilst there is an immediate improvement via the vitality domain of SF-36, this domain contributes relatively little to the overall utility scoring compared to domains which are likely to take longer for a patient to achieve a substantial change in score or reach their 'new normal' (i.e. physical functioning, physical role limitations, general health perceptions). Although the populations in the trials are similar to the UK population (17), country-specific differences in driving restrictions may have influenced quality of life. In the UK, the DVLA prevent patients with EDS and OSA from driving (18), thus the Company did not include the influence of road traffic accidents in their cost effectiveness analysis. However most patients were recruited from the United States where patients could continue driving despite their EDS. Driving has been identified as an important instrumental activity of daily living, and a systematic review of driving cessation showed that loss of driving ability was associated with substantially reduced quality of life in adults of similar age to the trial population (19). Therefore the impact on QoL in a US based population is unlikely to reflect the impact of improved EDS in a UK/EU cohort. During the appraisal of ID1065, the pitolisant ERG suggested that SF-6D may be more sensitive than EQ-5D in capturing QoL benefits (1). The pitolisant company provided a scenario that mapped ESS scores to SF-6D. The Committee for ID1065 agreed that the pitolisant company's scenario using SF-6D might be preferable, but stated that more understanding was needed to determine how well mapping to SF-6D captures quality-of-life benefits (1). The Committee for ID1065 concluded that it preferred the EQ-5D utility values derived from the clinical trials and that more detailed evidence should be provided to explain why EQ-5D is insensitive to capturing changes in a person's quality of life (1). Therefore, in the absence of appropriate HRQoL trial data, the Company maintain that the best method for describing the QoL improvement for patients with OSA is the use of the EQ-5D from the NHWS mapping formula in the base case, with an analysis using the McDaid algorithm provided in a scenario. Furthermore, it is likely that both generic measures underestimate the true relationship between ESS and utility. If the utilities from the time trade off study represent what this might look like in a real world setting, it suggests that the true ICERs for standard of care with the addition of solriamfetol vs standard of care without solriamfetol may be much lower than presented in this document. Following the ACD, the Company discussed with clinicians the topic of using health questionnaires to measure changes in QoL associated with changes in EDS (20). Based on these discussions, the Company's resolve in the use of the mapping approach was strengthened. Clinicians described a very substantial burden on QoL for patients with EDS. Note that these clinicians primarily specialised in narcolepsy but agreed that their responses could also be used to describe QoL for EDS due to OSA. In general, clinicians agreed with the shape of the NHWS and McDaid graphs, confirming they expected to see a correlating decrease in QoL as a patient's sleepiness increased. Clinicians highlighted that these are generic scales and not tailored for EDS, and the clinicians felt that these generic scales underestimate the true burden of EDS on QoL,	second-best option compared with using the available trial data, and the company did not provide the alternative SF-6D utilities. The FAD has been updated to reflect this – see FAD sections 3.9, 3.10, 3.11 and 3.12 for information on utilities.

Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
			thus the QALY gain with solriamfetol is likely an underestimate, as supported by the scenario using the time trade off study utility values.	
5.	Consultee	Jazz Pharmaceuticals	**Comment 5. On the conclusion that the range of dose split assumptions included in the company's and ERG's analysis is appropriateness** In all clinician interviews (both conducted prior to the submission and conducted post-ACD), clinicians consistently reported that the dose split would be determined by response rate, and that prescribers aim for the lowest effective dose (21). Due to the absence of pharmacotherapies licensed and indicated for the management of EDS due to OSA at the time of writing (24 June 2021), UK clinicians were unable to describe what the final dose split of solriamfetol 37.5, 75 and 150 mg may be in practice, but parallels can be drawn from clinicians' experience of prescribing drug therapy in narcolepsy. KOLs with experience in the use of wake promoting agents for managing EDS due to narcolepsy (21): • describe taking a cautious approach to titration, often with longer intervals than occurred in the trial • use descriptions including "start low" and "slow titration" to describe dosing At the time of the original company submission, early prescribing patterns from the US indicated a [redacted] dose split for the 37.5 mg/75 mg/150 mg solriamfetol doses, respectively. However, it is anticipated that UK prescribers will be more conservative than those of the US, and based on the anticipated UK prescribing approaches, the original base case assumed a dose split of 40/40/20. This may be considered a conservative approach given that in TONES 3 approximately 52% of patients on the 37.5 mg dose achieved normal ESS scores (ESS ≤10) by week 12 (22). It is expected that if a patient normalises on a given dose in clinical practice, that patient will remain on that dose (and would not unnecessarily titrate to a higher dose), thus in clinical practice half of patients may not titrate beyond the 37.5 mg dose. The anticipated prescribing patterns in the UK are consistent with early prescribing data from [redacted] (6). Note that as one 75 mg tablet can be split into two x 37.5 mg daily doses (7), a pack of 28 x 75 mg tablets will last twice as long for patients prescribed the lower 37.5 mg dose. Based on the above, it is anticipated that clinicians in the UK will slowly titrate solriamfetol starting at the lowest dose (37.5 mg) and the Company maintains that the standard approach in the UK would see the lowest available dose prescribed to the majority of patients. Although NICE and the ERG preference of a [redacted] dose split potentially sees too many patients titrating beyond the 37.5 mg dose, it is not inconsistent with the view that a low proportion of patients would receive the highest dose. Therefore, to align with the NICE & ERG preference the Company revised base case is set to a [redacted] dose split. However, the Company note per the ACD that "The Committee concluded that the range of dose split assumptions included in the Company's and ERG's analysis is appropriate to account for the variability in clinical practice."	Comment noted. The committee concluded that the dose split based on US prescribing data was acceptable for decision making. The FAD has been updated to reflect this – see FAD section 3.15 for more information on dose splits.

Therefore, the Company have provided all other dose split scenarios below (40/40/20, 33/33/33, and 20/40/40) with an investigation of the regression to the mean effect, as requested by the Committee, presented for each dose split analysis.

- Revised base-case results using [redacted] are presented in Section 0.
- Dose split scenarios are presented in Sections 0, 0, and 0

5.1. Revised base case results, dose split [redacted] for solriamfetol 37.5/75/150 mg

Table 5. 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	£4,810	11.524	30.213			
Standard of care with the addition of solriamfetol ([redacted] 37.5, 75, 150 mg)	[redacted]	11.969	30.213	[redacted]	0.445	[redacted]

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

Table 6. 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	£4,792	11.480	30.033			
Standard of care with the addition of solriamfetol ([redacted] 37.5, 75, 150 mg)	[redacted]	11.923	30.033	[redacted]	0.443	[redacted]

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

5.2. Dose split: 40/40/20 for solriamfetol 37.5/75/150 mg

Table 7. Dose split 40/40/20: revised base case

Technologies	Total costs (£)	Total QALYs	Total LYG	Incremental costs (£)	Incremental QALYs	ICER versus baseline (£/QALY)
Standard of care without solriamfetol	£4,810	11.524	30.213			
Standard of care with the addition of solriamfetol (40/40/20 37.5, 75, 150 mg)	[redacted]	11.935	30.213	[redacted]	0.411	[redacted]

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

Table 8. Dose split 40/40/20: observation bias analysis (ICERs)

		Regression to the mean						
		0%	5%	10%	15%	20%	30%	33%
True placebo	0%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	5%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	10%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	15%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	20%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	30%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	40%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	50%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	60%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	70%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
	80%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]		
	90%	[redacted]	[redacted]	[redacted]				
	100%	[redacted]						

Abbreviations: ICER, incremental cost effectiveness ratio.
Grey cells indicate implausible scenarios that exceed 100%.

5.3. Dose split: 33/33/33 for solriamfetol 37.5/75/150 mg

Table 9. Dose split 33/33/33: Revised base case

Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment

Technologies	Total costs (£)	Total QALYs	Total LYG	Incremental costs (£)	Incremental QALYs	ICER versus baseline (£/QALY)
Standard of care without solriamfetol	£4,810	11.524	30.213			
Standard of care with the addition of solriamfetol (33/33/33 37.5, 75, 150 mg)	[redacted]	11.988	30.213	[redacted]	0.464	[redacted]

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

Table 10, Dose split 33/33/33: observation bias analysis (ICERs)

		Regression to the mean						
		0%	5%	10%	15%	20%	30%	33%
True placebo	0%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	5%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	10%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	15%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	20%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	30%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	40%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	50%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	60%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	70%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	

Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment

	80%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]		
	90%	[redacted]	[redacted]	[redacted]				
	100%	[redacted]						

Abbreviations: ICER, incremental cost effectiveness ratio.
Grey cells indicate implausible scenarios that exceed the maximum 100%.

5.4. Dose split: 20/40/40 for solriamfetol 37.5/75/150 mg

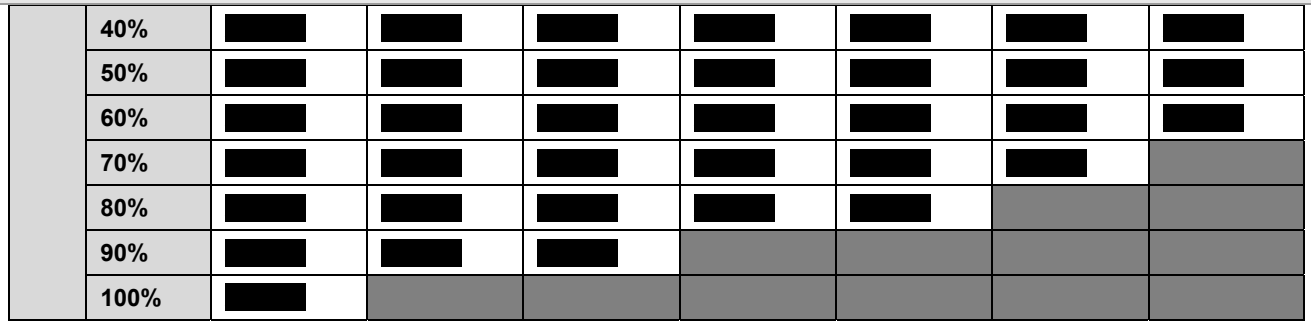
Table 11. Dose split 20/40/40: Revised base case results

Technologies	Total costs (£)	Total QALYs	Total LYG	Incremental costs (£)	Incremental QALYs	ICER versus baseline (£/QALY)
Standard of care without solriamfetol	£4,810	11.524	30.213			
Standard of care with the addition of solriamfetol (20/40/40 37.5, 75, 150 mg)	[redacted]	12.025	30.213	[redacted]	0.501	[redacted]

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

Table 12, Dose split 20/40/40: Observation bias analysis (ICERs)

		Regression to the mean						
		0%	5%	10%	15%	20%	30%	33%
True placebo	0%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	5%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	10%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	15%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	20%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	30%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
			 Abbreviations: ICER, incremental cost effectiveness ratio. Grey cells indicate implausible scenarios that exceed the maximum 100%	
6.	Consultee	Jazz Pharmaceuticals	**Comment 6. On the request to include hospitalisation costs for serious adverse events in the modelling** The Company welcome the consideration of the impact on hospitalisation rates of introducing solriamfetol into clinical practice and understand that the proposed use of the gross SAE-related hospital admission rate in TONES 5 by the ERG is a proxy for hospitalisations experienced in this population. In the ERG model, hospitalisation costs were estimated based on rates of SAE-related hospital admissions for patients with OSA in TONES 5. The ERG calculated that in TONES 5 [redacted]% ([redacted]) of solriamfetol-treated patients were hospitalised for SAEs. This included all events irrespective of a clear relationship to solriamfetol; only one such event was deemed treatment-related in TONES 5 (n=1 stroke [redacted] in the 150 mg arm). TONES 5 was a single arm, open label extension study, the data do not demonstrate *a difference* between the intervention (solriamfetol) and comparator (placebo), but instead only an absolute rate for solriamfetol and therefore the ERG analysis is limited by the assumption that all hospitalisations observed in TONES 5 would be incremental to SoC. This approach biases against solriamfetol in cost-effectiveness analyses and the Company are mindful that this is not consistent with NICE methodology, where it is the relevant cost *differences* between the intervention and comparator that need to be considered (2). Further, the NICE methods guide states RCTs are considered to be most appropriate for measures of relative treatment effect (2). As TONES 5 was a single arm, open label extension study, the data do not demonstrate *a difference* between the intervention (solriamfetol) and comparator (placebo), but instead only an absolute rate for solriamfetol. In the time since technical engagement and the NICE Committee meeting, the first Periodic Safety Update Report for solriamfetol has been considered by the EMA. The report spans [redacted] person-months ([redacted] person-months post authorisation) and considers that the number of adverse drug reactions in patients treated with solriamfetol in clinical practice is “relatively low”, which indicates that using the single-arm TONES 5 data in isolation likely over-estimates hospitalisation costs for this population. This further reinforces the robustness of the low AE rates for solriamfetol (including SAE and hospitalisation rates) observed in TONES 3, where it was compared with placebo. Furthermore, as outlined in the Company’s TE response Issue 8, Hospital Episodes Statistics (HES) data show that without exposure to solriamfetol in the real-world OSA population, hospitalisation rates overall are [redacted]% per annum (for	Comment noted. The committee considered the company scenario analyses and concluded that the rates presented in scenario 6.3 were acceptable for decision making. The FAD has been updated to reflect this – see FAD section 3.14 for more information on hospitalisation costs.

<table>
<tr><th>Comment number</th><th>Type of stakeholder</th><th>Organisation name</th><th>Stakeholder comment
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Please respond to each comment</th></tr>
<tr><td></td><td></td><td></td><td>
reasons other than sleep disorder), and hospitalisation for stroke – the only SAE deemed to be treatment-related in TONES 5 – occurs in [redacted]% per annum. As such, if TONES 5 had contained a control arm, it could be reasonably expected that these patients may also have experienced hospitalisations for adverse events, including stroke.
In order to maintain consistency with NICE methods to model comparative effects and to negate the limitations associated with using single-arm TONES 5 data, the Company revised base-case applies hospitalisation rates across the solriamfetol and SoC arms, based on annualised data from TONES 3. Rates are calculated from all SAEs which led to hospitalisation in each trial arm (solriamfetol; placebo), irrespective of a relationship to study drug, consistent with the approach adopted by the ERG for the ERG's analysis of TONES 5 solriamfetol data. Data utilised are presented in Table 13; as TONES 3 was a 12-week study, observed rates are converted to an annualised rate and applied on every model cycle. Note that the Company's revised base-case results are provided in Error! Reference source not found..

<u>Table 13: SAE-related hospitalisation from TONES 3 and applied in Company revised base-case</u>
<table>
<tr><th>Intervention</th><th>n/N</th><th>Rate, % Week 12</th><th>Rate, % annualised</th></tr>
<tr><td>SoC (placebo)</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td></tr>
<tr><td>Solriamfetol 37.5 mg</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td></tr>
<tr><td>Solriamfetol 75 mg</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td></tr>
<tr><td>Solriamfetol 150 mg</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td></tr>
</table>
Source: TONES 3 CSR Listing 14.3.16. Note that 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

As mentioned above, TONES 5 was a single arm, open label extension study, and as such, the data do not demonstrate a difference between the intervention (solriamfetol) and comparator (placebo), but instead only provide an absolute rate for solriamfetol. Therefore as per the NICE methods guide (2), the Company position is that the model should use the comparative, dose-specific data from the TONES 3 RCT.

However to allow investigation into the impact of SAEs, the Company also provide new scenario analyses accounting for the following:
• Section 0: any SAE-related hospitalisation for solriamfetol from TONES 5 vs zero rate for SoC (ERG preferred assumptions)
– In this scenario, TONES 5 SAE-related hospitalisation irrespective of relationship to study drug is modelled, as per ERG assumptions
◊ [redacted]% in the solriamfetol 150 mg arm, zero in other solriamfetol arms from TONES 5
1. Zero rate applied in the SoC arm
</td><td></td></tr>
</table>

- Section 0: any SAE-related hospitalisation for solriamfetol from TONES 5 vs HES rate for SoC
  - In the absence of data for SoC from the single-arm TONES 5 study, English HES data is modelled showing that [redacted]% of patients with OSA receiving SoC will be hospitalised per year *for reasons other than a sleep disorder*
    - ◊ [redacted]% in the solriamfetol 150 mg arm, zero in other solriamfetol arms from TONES 5
    2. [redacted]% from HES in the SoC arm

- Section 0: treatment-related SAE-related hospitalisation for solriamfetol from TONES 5 vs zero rate for SoC
  - In this scenario, the Company include only treatment-related SAEs leading to hospitalisation from TONES 5, which only included a single case of stroke in the solriamfetol 150 mg arm. This scenario may provide a more appropriate indication of incremental hospitalisation with solriamfetol over SoC than the ERG's preferred analysis. However, it should also be noted that hospitalisation for stroke is observed in the OSA population, as already highlighted above by the HES data.
    - ◊ [redacted]% in the solriamfetol 150 mg arm, zero in other solriamfetol arms from TONES 5
    - ◊ Zero rate applied in the SoC arm

6.1. Scenario analysis: ERG preferred assumptions for modelling hospitalisation costs

Table 14. Scenario analysis: any SAE related hospitalisation for solriamfetol from TONES 5 vs zero rate for SoC (ERG preferred assumptions)

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 ([redacted] 37.5, 75, 150 mg)	[redacted]	11.969	30.213	[redacted]	0.445	[redacted]

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

6.2. Scenario analysis: any SAE-related hospitalisation for solriamfetol vs HES rates for SoC

Scenario results are presented in Table 15. Despite the TONES 5 data showing fewer hospitalisations than found in a broadly matched population in HES (Patients with OSA), the Company have no evidence to suggest that solriamfetol is associated with a protective effect against hospitalisation, therefore this scenario is highly unlikely.

Table 15. Scenario analysis: any SAE-related hospitalisation for solriamfetol from TONES 5 vs HES rates for SoC

<table>
<tr><th>Comment number</th><th>Type of stakeholder</th><th>Organisation name</th><th>Stakeholder comment
Please insert each new comment in a new row</th><th>NICE Response
Please respond to each comment</th></tr>
<tr><td></td><td></td><td></td><td>
<table>
<tr><th>Technologies</th><th>Total costs (£)</th><th>Total QALYs</th><th>Total LYG</th><th>Incremental costs (£)</th><th>Incremental QALYs</th><th>ICER versus baseline (£/QALY)</th></tr>
<tr><td>Standard of care without solriamfetol</td><td>£8,884</td><td>11.524</td><td>30.213</td><td></td><td></td><td></td></tr>
<tr><td>Standard of care with the addition of solriamfetol ([redacted] 37.5, 75, 150 mg)</td><td>[redacted]</td><td>11.969</td><td>30.213</td><td>[redacted]</td><td>0.445</td><td>[redacted]</td></tr>
</table>
Abbreviations: ICER, incremental cost effectiveness ratio; LYG, life years gained; QALYs, quality adjusted life years.

6.3. Scenario analysis: treatment related SAE-related hospital admission rates for solriamfetol vs HES rates for SoC
Results are presented in Table 16.

Table 16. Scenario analysis: treatment-related SAE-related hospitalisation for solriamfetol from TONES 5 vs zero rate for SoC
<table>
<tr><th>Technologies</th><th>Total costs (£)</th><th>Total QALYs</th><th>Total LYG</th><th>Incremental costs (£)</th><th>Incremental QALYs</th><th>ICER versus baseline (£/QALY)</th></tr>
<tr><td>Standard of care without solriamfetol</td><td>£0</td><td>11.524</td><td>30.213</td><td></td><td></td><td></td></tr>
<tr><td>Standard of care with the addition of solriamfetol ([redacted] 37.5, 75, 150 mg)</td><td>[redacted]</td><td>11.969</td><td>30.213</td><td>[redacted]</td><td>0.445</td><td>[redacted]</td></tr>
</table>
Abbreviations: ICER, incremental cost effectiveness ratio; LYG, life years gained; QALYs, quality adjusted life years.
</td><td></td></tr>
<tr><td>7.</td><td>Consultee</td><td>Jazz Pharmaceuticals</td><td>Comment 7. On the potential increased resource use through a requirement for more monitoring of adherence to CPAP as noted by the clinical experts

In the ACD, the clinical experts noted that if solriamfetol were recommended, the likely requirement for more monitoring of adherence to CPAP could put pressure on services; the experts said that in most sleep clinics CPAP can be monitored</td><td>Comment noted. The committee considered the company's</td></tr>
</table>

Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
			remotely and acknowledged that although people having solriamfetol alongside a primary therapy such as CPAP would have their use monitored (i.e. within routine practice), it may have to be more frequent. The committee concluded that adherence to a primary therapy like CPAP is unlikely to be affected by treatment with solriamfetol, but more data are needed (3). The Company have considered this issue and provide additional information below to reassure the Committee that the introduction of solriamfetol will not put additional pressure on services. This additional evidence draws on the 2021 draft NICE guideline on obstructive sleep apnoea/hypopnoea syndrome (OSAHS), and its associated evidence reviews which help to address the proposed uncertainties surrounding the current treatment pathway, standards, and resource use for managing OSA, particularly in patients with persistent symptoms despite CPAP (23-25): • According to the evidence reviews supporting the development of these new guidelines, the "outcomes that matter most" in OSAHS include sleepiness scores (e.g. ESS) and systolic blood pressure for hypertension (24-26), and these outcomes are therefore important in the follow-up of patients with OSA. • In Evidence Review M the guideline committee noted that CPAP is just one aspect of the treatment for OSAHS, and that monitoring should be tailored to the person's overall treatment plan, which may include lifestyle changes and weight management, modifying sedative drugs and alcohol, stopping smoking, and treating underlying lung disease and other comorbidities. Additionally, Evidence Review M states that although control of symptoms is important, the committee agreed that treatment efficacy cannot be decided on improvements of symptoms alone as they are an imprecise indicator of treatment success (24). • Evidence Review N states that in current practice educational information is typically provided at an outpatient appointment 1 month after CPAP initiation and per annum thereafter, but that these appointments are not exclusively for providing education and support; e.g. during the appointment the sleep specialist would explore whether people with OSAHS have adequate control of their symptoms and whether further assistance is required to improve symptoms (25). The guideline committee agreed that providing education and support (i.e. to improve primary OSA therapy use) was reasonable as it can improve adherence and contribute to the cost-effectiveness of the intervention (25). Note that this is current practice for people newly provided with CPAP. • The draft guidelines recommend that patients with OSAHS are assessed for adequate control of symptoms at routine follow-up (according to the person's needs), and that annual follow-up should be considered once CPAP has been optimised (23). • In addition, the draft guidelines recommend that patients receiving CPAP for their underlying OSA receive telemonitoring (24). Telemedicine has been demonstrated to improve PAP compliance in patients with moderate to severe OSA (27), and in patients with OSA with high cardiovascular risk, telemonitoring is demonstrated to improve PAP compliance and patient-centred outcomes (28). As outlined in the solriamfetol summary of product characteristics (SmPC), the only monitoring requirements for solriamfetol are heart rate assessment and blood pressure measurement at treatment initiation, and periodic monitoring (7). These requirements are aligned with the proposed monitoring recommended within routine standard of care for OSA described in the draft NICE guideline (23).	analysis on adherence to primary OSA therapy, and concluded that adherence to primary therapy is unlikely to be affected by treatment with solriamfetol. The FAD has been updated to reflect this – see FAD section 3.5 for information on adherence to a primary OSA therapy

Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
			The Company sought the opinion of a range of clinicians practicing in England who describe a patient-centred approach to managing OSA, often with routine follow-up at approximately annual intervals. These experts suggest that patients with residual EDS may be followed up more frequently, consistent with the subsequently produced draft NICE guideline. Although it has been suggested that patients with residual EDS may be seen more regularly, as solriamfetol has been clinically demonstrated to reduce EDS in patients with OSA (5, 29), it is likely that its introduction into UK clinical practice may therefore reduce the overall burden of follow-up in this patient population. The development of the draft NICE guideline for OSAHS is independent of the ID1499 for solriamfetol and the guidelines are representative of monitoring of underlying OSA and primary OSA therapy by specialist teams. Once/if approved, these guidelines will form routine standard of care in the UK and would be applied in the management of OSA independently of solriamfetol prescribing. In following the recommendations in the guideline, patients with OSA using solriamfetol are **unlikely** to require additional resource use compared with patients who are not receiving solriamfetol, because all patients with OSA (regardless of solriamfetol use) will have their use of primary OSA therapy routinely monitored. Based on the above, the Company feel that the introduction of solriamfetol is unlikely to require any additional resource compared with current standard of care and future standard of care proposed in the draft NICE guideline for OSAHS.	
8.	Consultee	Jazz Pharmaceuticals	**Comment 8. On the request for sensitivity analysis to explore the impact of partner utilities using EQ-5D** Following the ACD, the Company discussed with clinicians the impact of EDS on partner QoL. From these discussions, the Company understand that there can be a significant impact on the partner. This impact on the partner was acknowledged in the ACDs for both ID1499 for solriamfetol in OSA and ID1065 for pitolisant (1, 3), and the Committee for ID1499 for solriamfetol in OSA concluded that partner utility values are important to consider (3). The impact of EDS on the partner of patients with OSA was described in Company submission Form B1.3, and Jazz completed an additional time trade-off study to demonstrate the benefit to the partner of treating the patients EDS. Given the acknowledgement by the Committee that the impact on partner utilities is important, the Company has repeated the original sensitivity analyses for the inclusion of partner utilities using the revised Company model. In these analyses, the patient utility values are mapped to create partner utility values using the time trade off study algorithm (described in Company Submission Form B.3.4.4.3). Results are presented in Table 17, Table 18 and Table 19. These data are presented so that the Committee can see the impact of including partner utilities on the ICER. However, as the Committee believed that the time trade off study provided insufficient evidence to warrant inclusion in the modelling, the company has excluded this QALY gain due to improvements in partner utility from the revised base case (note that partner utilities were previously excluded from the original company base case, and were presented as scenario analyses only). Given the above, the exclusion of partner utilities from the total QALY gain with solriamfetol represents a conservative approach and therefore the ICERs presented for the base case analysis would likely underestimate the cost-effectiveness of solriamfetol in managing EDS. It is unclear why the Committee believes the time trade off study provides insufficient evidence to warrant inclusion in the modelling. Unfortunately, at this stage of the STA process, the Company have insufficient time with which to carry out an additional study using an alternatively methodology (e.g. EQ-5D) that may provide more robust evidence on the impact of EDS on the partner.	Comment noted. The FAD has been updated to reflect this – See FAD section 3.13 for information on partner utility values, and FAD section 3.18.

Table 17. Scenario analysis: NHWS mapping patient utilities combined with partner utilities

Technologies	Total costs (£)	Total QALYs	LYG	Incremental costs (£)	Incremental QALYs	Incremental ICER
Standard of care without solriamfetol	£4,810	20.605	30.213			
Standard of care with the addition of solriamfetol ([redacted] 37.5, 75, 150 mg)	[redacted]	**21.214**	**30.213**	[redacted]	**0.609**	[redacted]

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

Table 18. Scenario analysis: McDaid mapping patient utilities combined with partner utilities

Technologies	Total costs (£)	Total QALYs	LYG	Incremental costs (£)	Incremental QALYs	Incremental ICER
Standard of care without solriamfetol	£4,810	23.943	30.213			
Standard of care with the addition of solriamfetol ([redacted] 37.5, 75, 150 mg)	[redacted]	**24.467**	**30.213**	[redacted]	**0.524**	[redacted]

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

Table 19. Scenario analysis: time trade off patient utilities combined with partner utilities

Technologies	Total costs (£)	Total QALYs	LYG	Incremental costs (£)	Incremental QALYs	Incremental ICER
Standard of care without solriamfetol	£4,810	21.296	30.213			
Standard of care with the addition of solriamfetol ([redacted] 37.5, 75, 150 mg)	[redacted]	**22.599**	**30.213**	[redacted]	**1.303**	[redacted]

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

Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
9.	Consultee	Jazz Pharmaceuticals	**Comment 9. On the conclusion that solriamfetol treatment is likely to be limited to secondary care but more information is needed** The committee concluded that solriamfetol treatment is likely to be limited to secondary care, but more information is needed (3). The summary of product characteristics for solriamfetol state that treatment with solriamfetol requires specialist initiation (7). Further, it is common for patients with OSA to remain within secondary and sometimes tertiary care, given the nature of the disease. In addition, as a newly licensed medication, solriamfetol carries a black triangle, severely limiting (in many cases precluding) its use in primary care at this time. The restriction of solriamfetol to secondary care is consistent with the anticipated prescribing of pitolisant hydrochloride in secondary care per the ACD for NICE ID1065 (1). Discussions with NHS stakeholders (clinicians and pharmacists) revealed the preferred route for continuation of prescribing of solriamfetol is outsourced outpatient pharmacy from secondary care; some areas will prefer to adopt NHS contracted homecare medicines services. Dr Sonya Craig's clinical expert statement, representing the British Thoracic Society, stated "It is very unlikely that primary care would be willing to take on prescribing of this drug" (17). NHSE Specialist Pharmacy Service has published clear principles on routes of supply for medicines to outpatients, ratified by the Regional Medicines Optimisation Committee (RMOC) (30). The document uses sodium oxybate (a medication used by sleep services) as an example of a drug that is suitable for Outsourced Outpatient Dispensing (OOPD) or Homecare Delivery for continuation of prescribing to outpatients. During the COVID-19 pandemic, many OOPD services have been couriering drugs to patients. In discussions with NHS customers, these routes have been validated as well-suited for solriamfetol. In addition, solriamfetol is listed as a restricted 'Red' drug in formularies, meaning its prescription is limited to hospital only (31-34). In alignment with its secondary care prescribing, Jazz has listed the price of solriamfetol in the BNF and on DM&D as 'hospital only' (35).	Comment noted. The committee considered the evidence provided by the company that solriamfetol is likely to be limited to secondary care. The FAD has been updated to reflect this – See FAD section 3.3 for information on solriamfetol prescribing setting.
10.	Consultee	Jazz Pharmaceuticals	**On the committee's statement that there is a high level of uncertainty in the analyses, and an acceptable ICER is below £20,000 per QALY gained** In ACD 3.15, the Committee felt that was a high level of uncertainty around the ICERs, in particular: • the effect of solriamfetol on adherence to primary obstructive sleep apnoea therapy • whether changes in quality of life were adequately captured by mapping the ESS to the EQ-5D • the adjustment for the placebo effect • the dose splits that will be used in clinical practice In order to increase the certainty surrounding the ICERs presented, and in particular the issues listed above, the Company has now provided comment or additional analyses in their response to ACD. The extensive clinical evidence demonstrating the placebo effect is not a regression to the mean (Section 0), in combination with sensitivity analyses on adherence to primary OSA therapy (Section **Error! Reference source not found.**), new analyses on the cost-effectiveness of solriamfetol in patients who are CPAP intolerant (Section 0), new dose split analyses (Section **Error! Reference source not found.**) indicate that solriamfetol is a cost-effective treatment for managing EDS due to OSA at the lower threshold of £20,000.	Comment noted. The committee considered the additional evidence provided by the company. Uncertainty remained around how the quality of life benefit of solriamtefol was measured and the adjustment for

<table>
<tr><th>Comment number</th><th>Type of stakeholder</th><th>Organisation name</th><th>Stakeholder comment
Please insert each new comment in a new row</th><th>NICE Response
Please respond to each comment</th></tr>
<tr><td></td><td></td><td></td><td>The Company feels given the increased certainty surrounding these issues through the additional data and responses provided in the Company's ACD response, a threshold higher than £20,000 per QALY gained could be acceptable. The introduction of the new solriamfetol PAS price substantially reduces the ICERs to below the proposed acceptable threshold of £20,000 per QALY gained in the base case, and are therefore reassuringly cost-effective if considering thresholds higher than £20,000 per QALY.
The results of an updated probabilistic sensitivity analysis (PSA) based on the Company's revised model are presented below. The probability that solriamfetol would be the most cost-effective treatment was 75% at a threshold of £20,000 per QALY, and was 99% at a threshold of £30,000 per QALY (Figure 1). Across 5,000 PSA simulations, solriamfetol was associated with a mean cost of £[redacted] (95% CI: [redacted]) and mean total QALYs of 12.398 (95% CI: 12.387, 12.408) (Table 20). These results are highly congruent with the deterministic results. Overall, the results remain consistent with the base case analysis.

Figure 1. Cost-effectiveness acceptability curve
 
Table 20. Probabilistic sensitivity analysis results
<table>
<tr><th>Technologies</th><th>Total costs (£)</th><th>Total QALYs</th><th>Incremental costs (£)</th><th>Incremental QALYs</th><th>ICER incremental (£/QALY)</th></tr>
<tr><td>Standard of care without solriamfetol</td><td>£4,873 (£4,782 - £4,964)</td><td>11.866 (11.855 - 11.877)</td><td></td><td></td><td></td></tr>
</table></td><td>the improvement in the control arm of TONES 3. Because of this, the committee concluded that an acceptable ICER would be at the lower end of the range that NICE normally considers an acceptable use of NHS resources. The FAD has been updated to reflect this – See FAD section 3.16 for information on the cost-effectiveness estimates.</td></tr>
</table>

Standard of care with the addition of solriamfetol (XXXXX 37.5, 75, 150 mg)	[redacted]	12.398 (12.387 - 12.408)	[redacted]	0.531	[redacted]

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

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11	Consultee	Jazz Pharmaceuticals	**On restricting solriamfetol to patients with ESS > 12 in the Company base case** Section 3 of the ACD states: "It agreed that a subgroup of people with a baseline Epworth Sleepiness Scale (ESS) score of 12 should be used in the modelling (see technical report issue 2)." The discussion that took place in the Committee meeting resulted in agreement that the baseline ESS that should be used in the modelling is ESS >12. A follow-on discussion between NICE and the Company on 19 April 2021 confirmed that the baseline ESS of >12 should be used in the modelling. This amendment is reflected in the Company's revised model and CE analyses.	Comment noted. The FAD has been updated to reflect this – see FAD section 3.7 for information on the definition of treatment response .
12	Consultee	Jazz Pharmaceuticals	**On the Committee's description of CPAP as a comparator for solriamfetol** ACD 3.2 states "3.2 The Committee concluded CPAP is an appropriate comparator, but some people cannot tolerate it." This is contradictory to the rest of the ACD discussion where the comparison is described as (i) CPAP plus solriamfetol vs (ii) CPAP plus no additional intervention. Further, section 3.3 of the ACD states "The Committee concluded that the clinical and cost-effectiveness evidence submitted by the Company does not cover the full marketing authorisation." Here the comparison is now described as (i) no use of CPAP plus solriamfetol only vs (ii) no use of CPAP plus no additional intervention. Thus, the statement "The Committee concluded CPAP is an appropriate comparator" is contradictory. Note that the Company has provided new analysis in Section 0 of this ACD response, which demonstrate that solriamfetol is cost-effective both for the patients using vs not using a primary OSA therapy.	Comment noted. The FAD has been updated to reflect this – see FAD section 3.2 for information on comparators.
13	Consultee	Jazz Pharmaceuticals	**On the ERG's comment that it is difficult to interpret the TONES clinical evidence demonstrating the placebo effect is unlikely regression to the mean** In the ERG Response to TE Issue 4, Section 2.4, the ERG stated "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". The data referred to by the ERG were important clinical evidence demonstrating that regression to the mean was not responsible for the placebo effect observed in TONES 3. Therefore, this clinical data from patients with OSA who were enrolled in TONES 3 or TONES 4 and then subsequently enrolled in TONES 5 have been re-examined and a new explanation of the data is provided in the below sections.	Comment noted. The committee considered the company's evidence regarding the improvement in the control arm of TONES 3. It

Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
			This extensive examination of clinical data provides strong evidence that the placebo effect observed in TONES 3 is not regression to the mean, consistent with comments by the ERG, clinical experts and Committee (3, 17): • ERG report section 4.2.6.2 states "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." • ACD 3.9 states "The clinical experts advised that a placebo effect is common in trials in this disease area and suggested it could have occurred in the TONES 3 placebo with standard care group". **Summary of trial design for TONES 3, TONES 4 and TONES 5** 1. TONES 3 was the pivotal 12-week placebo-controlled randomised controlled trial for solriamfetol in treating EDS due to OSA (Section 0). 2. TONES 4 (n=122) was a 6-week study of solriamfetol for patients with OSA, comprised of a 2-week titration phase (all patients undertake solriamfetol titration), 2-week stable dose phase (all patients receive stable dose solriamfetol), and 2-week double-blind randomised withdrawal phase (patients randomised 1:1 to receive placebo or continue stable dose solriamfetol). 3. TONES 5 was an open label extension study that enrolled patients who had previously completed another TONES study. These patients can be categorised into two groups: a. Patients with OSA who had completed a prior TONES study (i.e. TONES 3) and immediately enrolled into TONES 5 (n=333) b. Patients with OSA who had completed a prior TONES study (i.e. TONES 4) but had a break in solriamfetol treatment of varying durations before enrolling into TONES 5 (n=84) **Clarification of the description of TONES 5 trial in ACD 3.9** ACD 3.9 states: "During TE, the Company presented evidence to suggest there was no regression to the mean. This included evidence from people transitioning from TONES 3 to TONES 5, a 52-week open-label trial assessing solriamfetol's long-term effectiveness. It included a 2-week placebo-controlled randomised withdrawal phase for patients moving from other TONES trials into TONES 5." This statement requires clarification: *all of the patients* in TONES 5 had completed a prior TONES study and therefore the randomised withdrawal phase was not restricted to any specific subgroup of patients. Further, note that patients who completed the 12-week TONES 3 study *immediately* enrolled into TONES 5 thus continued solriamfetol for only 40 weeks in TONES 5 (i.e. for a total of 52 weeks). This differs from patients who had completed a prior TONES study and had a break in treatment prior to TONES 5 who were required to complete 52 weeks of treatment within TONES 5 (29).	concluded that it was unlikely that regression to the mean was a major cause of the improvement in the TONES 3 control arm. The FAD has been updated to reflect this – see FAD section 3.8 for information on the different mechanisms for the improvement in the control arm of TONES 3.

			Evidence from patients completing TONES 3 and subsequently enrolling in TONES 5 indicates that the placebo effect is more likely to be true placebo than regression to the mean A total of [redacted] patients with OSA who completed TONES 3, immediately enrolled in TONES 5; the ESS scores for these patients transitioning between the trials provides evidence against a regression to the mean (Figure 2). • Patients in TONES 3 who were randomised to solriamfetol (orange line) achieved substantial improvements (i.e. reduction) in mean ESS. When these patients moved into the open label and unblinded TONES 5 trial, their ESS score further improved (i.e. reduced). • Patients who were randomised to placebo (blue line) had improvements (i.e. reduction) in mean ESS at a smaller level compared with solriamfetol, but when these patients moved into the open label and unblinded TONES 5, they achieved rapid improvements (i.e. reduction) in ESS. • The trend line for ESS reduction upon starting solriamfetol treatment in both TONES 3 and TONES 5 as shown in Figure 2 is highly similar, and furthermore is similar to that observed for patients both upon starting solriamfetol in TONES 4, and restarting solriamfetol upon enrolling into TONES 5 (discussed in detail in 0 and shown in Figure 3). • The additional improvements (i.e. reduction) of ESS scores when patients are receiving unblinded compared with blinded solriamfetol treatment is further evidence that the effect observed in the placebo arm is not a regression to the mean. If this were a regression to the mean, the ESS scores would trend towards a reduction (i.e. improvement) in ESS value over time, however this slow improvement in ESS after week 1 in TONES 3 is observed at a similar rate in both the placebo and solriamfetol arms, indicating this is not a regression to the mean. **Figure 2. ESS scores for patients with OSA who completed TONES 3 and subsequently enrolled into TONES 5**	

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			 * All patients in TONES 5 received solriamfetol 75, 150 or (unlicensed) 300 mg; Investigators were instructed to titrate subjects to the maximal dose of solriamfetol that was tolerated to maximise therapeutic efficacy. **Evidence based on patients moving from TONES 4 into TONES 5 demonstrates that the placebo effect highly unlikely to be driven by regression to the mean** A total of [redacted] patients who completed TONES 4 subsequently enrolled in the open label TONES 5 open label extension study after a break in treatment (as they stopped treatment upon completing TONES 4). The break in treatment between completing TONES 4 and enrolling in TONES 5 is unknown.	

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			Figure 3 presents the mean ESS scores for these [redacted] patients throughout TONES 4 and subsequently throughout TONES 5. • In TONES 4 (left panel), all patients received solriamfetol during the titration and stable dose phases (first four weeks) and had a significant reduction (i.e. improvement) in mean ESS scores. • During the two-week randomised withdrawal phase (weeks 4 to 6) in TONES 4, patients randomised to placebo (blue line) experienced an increase (i.e. deterioration) in mean ESS, but patients randomised to continue solriamfetol (orange line) experienced no change in ESS score. • At the end of the randomised withdrawal phase, mean ESS scores were placebo=[redacted] and solriamfetol=[redacted]. Upon completing TONES 4, these patients stopped receiving solriamfetol and after a break in treatment (duration unknown), subsequently enrolled into TONES 5 (right panel). • A comparison of the mean ESS scores in TONES 4 vs TONES 5 shows that the baseline ESS scores for each trial fall within [redacted] point of each other: – For patients in TONES 4 who received placebo during the randomised withdrawal phase, baseline ESS in TONES 4 vs TONES 5 were [redacted] vs [redacted], respectively – For patients in TONES 4 who continued solriamfetol during the randomised withdrawal phase, baseline ESS in TONES 4 vs TONES 5 were [redacted] vs [redacted], respectively • The similarity between baseline ESS scores indicates that neither baseline was a temporary extreme value (as would be expected if there were regression to the mean), but instead both reflect a true mean ESS for these patients. In addition to indicating that the effect observed in the placebo arm of TONES 4 is not a regression to the mean, these data also demonstrate that patients who discontinue and subsequently restart solriamfetol can achieve repeat reductions (improvements) in ESS with rapid onset. As shown in Figure 3, after discontinuing solriamfetol treatment due to completing TONES 4, patients' ESS returned towards baseline. Within two weeks of restarting solriamfetol treatment in TONES 5, the patients experienced significant reductions (i.e. improvements) in mean ESS scores in TONES 5, with mean ESS scores reduced (improved) to levels similar to those previously achieved in TONES 4. **Additional evidence from TONES 4 demonstrating that the placebo effect is highly unlikely to be driven by regression to the mean** In TONES 4, patients randomised to continue solriamfetol treatment during the randomised withdrawal phase did not experience an increase in ESS score ([redacted] at week 4 vs [redacted] at week 6). Note that these patients did not exhibit a 'nocebo' effect – a psychological negative patient expectancy that their symptoms will worsen as a result of believing they were randomised to placebo (despite being randomised to active treatment) (36); treatment effect with solriamfetol is therefore robust to this neurobiological phenomenon. Conversely, patients who were randomised to switch to placebo during the randomised withdrawal phase experienced a rapid increase in ESS scores upon switching to placebo and withdrawing from solriamfetol (from [redacted] at week 4 to [redacted] at week 6). The ESS scores for patients randomised to placebo (i.e. to withdraw from solriamfetol) returned toward an average ESS consistent with their baseline characteristic ESS. Subsequently, at the baseline of TONES 5, the mean ESS	

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			score for these patients was [redacted], demonstrating that with extended durations after solriamfetol withdrawal, patients eventually returned to a pre-treatment, true baseline ESS score. The extensive clinical data presented above support a true placebo effect *and* a stable underlying disease state with consistent baseline ESS; unless the nadir of natural variation in reported symptom severity happened to coincide perfectly with baseline ESS assessments in *both* TONES 4 and TONES 5. It is therefore highly unlikely that a regression to the mean contributed to the placebo effect. **Figure 3. ESS scores over time for patients with OSA who completed TONES 4 and subsequently enrolled in TONES 5**  Abbreviations: ESS, Epworth Sleepiness Scale; RW, randomised withdrawal phase. a All patients were receiving solriamfetol from baseline to week 4 and then randomised 1:1 to solriamfetol or placebo (37).	

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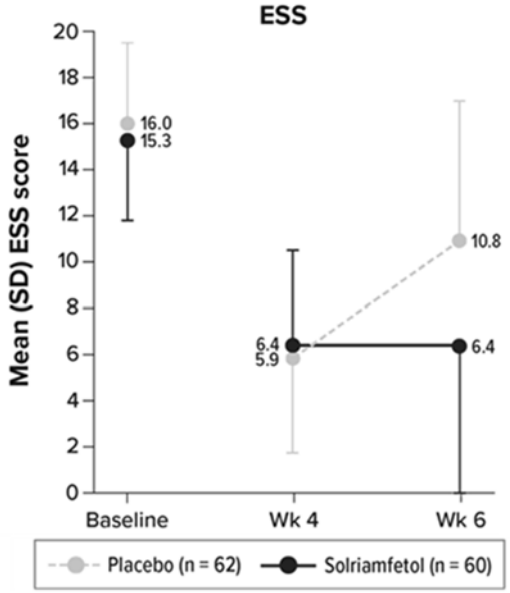
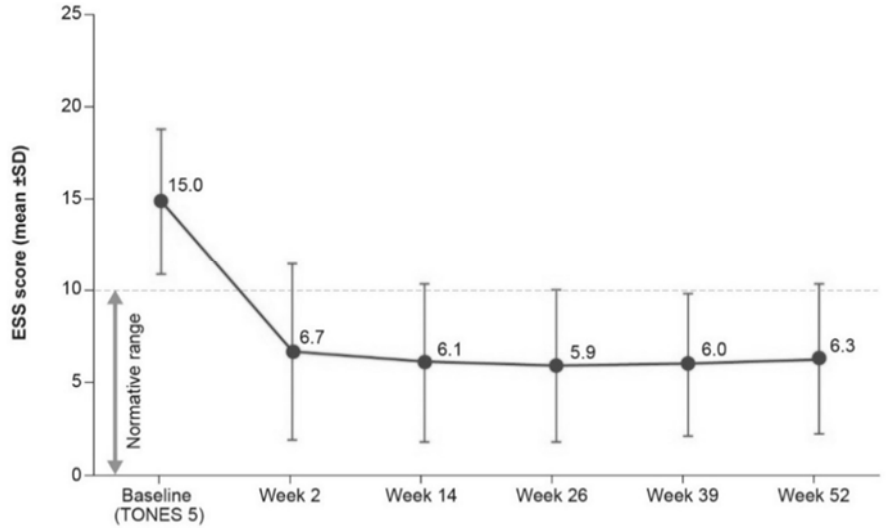
			Baseline characteristics of the safety population in TONES 4 (ie, any participant who received ≥1 dose of solriamfetol in the titration phase) were consistent across the three phases of the study and were comparable between groups. ESS score ranges from 0–24 where higher scores indicate higher levels of sleepiness, and ESS ≤ 10 are considered within the normal range. The randomised withdrawal phase of TONES 5 is not shown however results were similar to TONES 4 In ERG Response to TE, Issue 4, Section 2.4, the ERG stated that "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" and 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". Although the population may have been open to selection bias, this was not a pre-specified analysis in the trial, however note that approximately [redacted]) of patients in TONES 4 subsequently enrolled in TONES 5, and these [redacted] patients formed the majority of the patients in TONES 5 Group B (Total patients in Group B =84; i.e. those patients who enrolled into TONES 5 following a break in treatment after completing a prior TONES study) (29). The ESS efficacy results for these [redacted] patients in TONES 4 (Figure 3) was broadly comparable to the TONES 4 overall results (Figure 4), and the efficacy for these patients in TONES 5 was broadly comparable to the TONES 5 overall results (Figure 5).	

Figure 4. TONES 4: ESS at baseline and before/after 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 (37).

Figure 5. 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 2020 (29)

Evidence from patients who completed TONES 3 and TONES 4 who had both a screening and baseline ESS assessment for TONES 5

As mentioned above, TONES 5 was an open label extension study that enrolled patients who had previously completed another TONES study. A small group of patients who previously completed TONES 3 and TONES 4, and subsequently enrolled in TONES 5, had both a screening and a baseline ESS score for TONES 5 (Table 21; duration of time between assessments is unknown):

- For the 10 patients in TONES 3 with both measurements, mean ESS was [redacted] at screening and [redacted] at baseline
- For the 14 patients in TONES 4 with both measurements, mean ESS was [redacted] at screening and [redacted] at baseline

Table 21. Mean ESS scores at screening and baseline assessments in TONES 5, for patients who completed TONES 3 and TONES 4 and subsequently enrolled into TONES 5

	ESS score at screening assessment in TONES 5	ESS score at baseline assessment in TONES 5
TONES 3 (N=10)		
Mean (SD)	[redacted]	[redacted]
Median (Range)	[redacted]	[redacted]

Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment

TONES 4 (N=14)		
Mean (SD)	[redacted]	[redacted]
Median (Range)	[redacted]	[redacted]

Abbreviations: SD, standard deviation.
N numbers reflect the patients from each trial that had both a screening and baseline ESS score for TONES 5.
Duration of time between screening and baseline assessment of ESS is unknown.

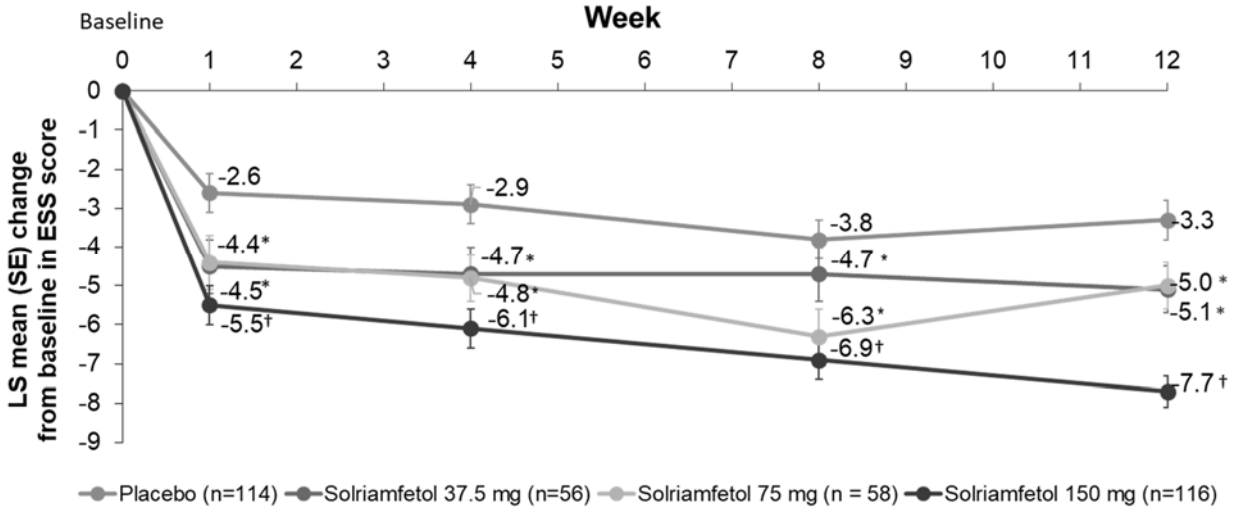
The screening and baseline ESS scores for these patients fall within [redacted] point of each other (within each trial cohort), and are within ~1 point of the respective trial population means (TONES 3: placebo 15.6; solriamfetol 15.2; TONES 4: overall 15.4) (37). This demonstrates the relative stability of mean ESS scores over time (consistent with the evidence in Figure 3), and indicates that the mean ESS reductions observed in the placebo arms are unlikely to be regression to the mean. Consistent with this, Jazz consulted a range of clinical experts on the natural variation in EDS as measured by ESS, and the clinicians informed us that in general it was expected that ESS would remain stable based on validated reproducibility in the clinical trial setting, that patients experience a sustained benefit from CPAP over time, and that any changes can be generally be attributed to non-OSA factors such as treatment or onset of depression, onset of periodic limb movement disorder (38).

The speed of placebo response is inconsistent with regression to the mean

The onset of the placebo effect observed in TONES 3 was rapid, occurring within the first week of the trial, and continuing to improve over subsequent time points. If regression to the mean were responsible for the improvements in ESS scores in the placebo arm, it is highly unlikely that this would occur in the first week as regression to the mean is expected to occur over a longer period of time.
Furthermore, in considering the patient journey, the duration of time that would pass from a patient entering a temporary acute worsening of their ESS through to receiving placebo in the study suggests the placebo effect in the TONES trials are unlikely to reflect a regression to the mean:

1. A patient with diagnosed OSA notices that their residual EDS is having an acute, severe impact on their life
2. The patient makes a decision to enrol in a clinical trial for treatment for their residual EDS
3. Patient potentially consults their own primary or secondary care doctor treating their diagnosed underlying OSA
4. Patient is screened and enrolled in the trial
5. Patient receives placebo in the trial

Steps 1 to 5 above are likely to require an extended duration of time, thus it is unlikely the patients receiving placebo would subsequently experience a rapid reduction (i.e. improvement) in ESS within the first week of the trial (**Error! Reference source not found.**), and continue to improve over the following 11 weeks.

Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
			This rapid onset of effect is also observed in TONES 4 (Figure 4) and combined with the evidence presented in Section 0 indicates that the baseline ESS scores in the trials are reflective of a true mean baseline and that regression to the mean is not contributing to the improvements in ESS observed in the placebo arm. **TONES 3: Change from baseline on the ESS at weeks 1, 4, 8, and 12 (mITT Population)**  Abbreviations: LS, least squares; ESS, Epworth Sleepiness Scale; mITT, modified intent to treat; MMRM, mixed effects repeated measures; SE, standard error. *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. **Conclusion** Following extensive examination of the TONES programme clinical data, the data show that there is little evidence to support the presence of a regression to the mean effect in the trials. Instead the data presented support a true placebo effect *and* a stable underlying disease state with consistent baseline ESS. Unless the nadir of natural variation in reported symptom severity happened to coincide perfectly with baseline ESS assessments in *both* TONES 4 and TONES 5, it is therefore highly unlikely that a regression to the mean contributed to the placebo effect. As such, the assumption of a Hawthorne effect in the Company's base case analysis (**Error! Reference source not found.**) can be considered a conservative approach that likely underestimates the true cost-effectiveness of solriamfetol.	

Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
14	Consultee	British Thoracic Society	We note that the following reference has not been included: Effects of Solriamfetol on Quality-of-Life Measures from a 12-Week Phase 3 Randomized Controlled Trial Terri E. Weaver et al Annals ATS Volume 17 Number 8 August 2020	Comment noted.
15	Consultee	British Thoracic Society	The provisional recommendations are appropriate.	Comment noted.
16	Web comment	Patient 1	I am disappointed to hear that the provisional decision is that solriamfetol will not be made available on the NHS. I am a sleep apnoea sufferer myself who, despite high usage of CPAP, finds myself continuing to experience fatigue, and was informed by my consultant that this drug may be available going forward. One thing that does seem to have been overlooked is the fact that currently other than CPAP there is nothing that the NHS can offer patients if CPAP fails to remedy their issues. Modafinil used to be available on the NHS but this was withdrawn long before I (and others) were diagnosed, meaning it's not readily available to patients like me. Additionally, modafinil can't always be tolerated by people. I paid out of my own pocket to be able to try the drug and it worked for a period of time, but it eventually stopped working, so to have solriamfetol available for people to try would give patients options. Whilst I understand NICE's concerns around the cost of the drug, you need to bear in mind that if the cost is prohibitive for the NHS then it certainly would be for patients also - the NHS, through economies of scale, would be able to secure the drugs cheaper than a patient would and it's not going to be affordable to patients otherwise. Rather than preventing the people who need it from accessing the drug, a far better system would be to only offer it to those who can demonstrate they still have issues even when they have high usage of CPAP. I know that I have already gotten my CPAP usage as high as it can go, as I'm using it most nights but sometimes I can fall asleep without it as I'm too tired to put my mask on or I take it off mid-sleep without being awake enough to realize. Remember also that whilst there may be an upfront cost for this drug to the NHS, sleep apnoea is linked to many adverse impacts for individuals - for example, many patients struggle to exercise regularly due to fatigue which can lead to all manner of health issues - so the NHS would see a cost for having to treat those patients. I personally have noticed that my lifestyle has been less active since my diagnosis. The fatigue can be crippling - I often have to have mid day naps just to get through day but often these sleeps are unrefreshing leaving me feeling no better even after the nap. It's not an understatement to say that I have not been able to have a normal life since my diagnosis. Whilst there is often an assumption that this is an illness that only affects the old or overweight, I was diagnosed in my mid-twenties at a normal BMI, so there are young people who's life is being ruined by this condition. The fact that I need the CPAP equipment anytime I sleep acts as an extra barrier to having a normal life as it is something I need with me always. If I have to go somewhere and can't take my CPAP with me then my condition would deteriorate worse than it already is, each day that I didn't use the machine. To have a drug that I could take when CPAP is not an option would improve my quality of life. Whilst people often think sleep apnoea is something minor that can be remedied, the truth is that it's a serious condition whereby you can stop breathing in your sleep, leaving you drained the next day with headaches and other symptoms and yet there are no drugs available at the moment on the NHS for it. I believe making solriamfetol available would help improve the quality of life of many sleep apnoea sufferers. I hope the decision will be reconsidered.	Comment noted. The committee acknowledged the impact of OSA on quality of life (see FAD section 3.1). It appraised solriamfetol within its marketing authorisation for improving wakefulness and reducing excessive daytime sleepiness in adults with OSA whose excessive daytime sleepiness has not been satisfactorily treated by primary OSA therapy such as CPAP. Deciding which treatments to recommend

Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
				involves balancing the needs and wishes of individuals and the groups representing them against those of the wider population. This sometimes means treatments are not recommended because they do not provide sufficient benefit to justify their cost ('The principles that guide the development of NICE guidance and standards, principle 5 and principle 7).
17	Web comment	Patient 1	Disability discrimination - there are many people who cannot work or live normal lives due to sleep apnoea and co-morbidities so without offering any care, beside CPAP, that leaves people without any options.	Comment noted. The NICE recommendation applies to the whole patient group covered by the marketing authorisation and there is no less favourable treatment for

				reasons related to a person's disability. The Committee had due regard for the impact of the guidance on patients and considered many factors, including the impact of the condition and technology on quality of life, the innovative nature of the treatment and likely non-health-related benefits. Despite this, the cost-effectiveness estimates for solriamfetol were higher than the range normally considered acceptable. In fulfilling NICE's function to appraise the clinical and cost effectiveness of healthcare technologies and ensure effective use of healthcare resources, the Committee were not able to recommend the

Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
				use of solriamfetol.

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

Consultation on the appraisal consultation document – email: **NICE DOCS**

Please read the checklist for submitting comments at the end of this form. We cannot accept forms that are not filled in correctly.

The Appraisal Committee is interested in receiving comments on the following:

- has all of the relevant evidence been taken into account?
- are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?
- are the provisional recommendations sound and a suitable basis for guidance to the NHS?

NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that the preliminary recommendations may need changing in order to meet these aims. In particular, please tell us if the preliminary recommendations:

- could have a different impact on people protected by the equality legislation than on the wider population, for example by making it more difficult in practice for a specific group to access the technology;
- could have any adverse impact on people with a particular disability or disabilities.

Please provide any relevant information or data you have regarding such impacts and how they could be avoided or reduced**.**

Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	Jazz Pharmaceuticals UK Ltd
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	None
Name of commentator person completing form:	Dr Patricia Keegan

1. Executive Summary

Following advice from NICE and the ERG, the Company has improved its model, the new results of which indicate that solriamfetol is a cost-effective treatment to improve wakefulness and reduce excessive daytime sleepiness in adults with OSA whose sleepiness has not been satisfactorily treated by primary OSA therapy. The Company has also provided evidence which indicates solriamfetol is a cost-effective treatment for patients unable to tolerate primary OSA therapy (i.e. CPAP, oral devices). Additional analyses and evidence have increased the certainty of the ICERs presented. The following key topics have been addressed:

- The revised base case ICER is likely to be an overestimate due to an underestimate of the improvement in QoL with solriamfetol, the exclusion of the QoL impact on partners, the use of the Hawthorne effect rather than the true placebo effect, and the overestimation of the number of patients on higher doses of solriamfetol.
- The placebo effect in TONES 3 is unlikely to be accounted for by regression to the mean and even when a contribution from regression to the mean is included, solriamfetol remains cost-effective. Solriamfetol is unlikely to have an effect on adherence to primary OSA therapy.

1.1. Company's Revised Model

In response to the advice received from NICE and the ERG through the appraisal consultation document (ACD), the Company has identified ways in which the company's model could be further improved. Details of these changes are provided in this response document.

Following the initial appraisal committee meeting (March 2021), the Company has revised some of the model assumptions in order to:

- Include a new Patient Access Scheme (PAS) price for solriamfetol
- Align with the ERG and NICE advice
- Reflect patient input from the Committee meeting
- Avoid creating clinically implausible model scenarios
- Align with the ACD for ID1065 for pitolisant (1)
- Ensure the revised model continued to be consistent with NICE methods (2)

In ACD 3.10 the Committee was concerned about the validity of some outputs generated by the ERG's model (3). For example, the Committee noted that the level of response in the ERG's standard of care (SoC) alone group, and the difference between the two groups (Soc alone vs SoC with solriamfetol) were implausible. The Company agrees with the concerns raised by the Committee, and therefore the Company's revised model continues to use a three health state approach (responder, non-responder, dead).

The base case results using the company's revised model are presented in Table 1, with a full list of assumptions and the associated rationale presented in Table 2. Where the Company's response to ACD in the sections below contain additional information related to the company's revised model assumptions, Table 2 also contains a signpost to this additional content.

Table 1. Revised base case results

Technologies	Total costs (£)	Total QALYs	Total LYG	Incremental costs (£)	Incremental QALYs	ICER versus baseline (£/QALY)
Standard of care without solriamfetol	£4,810	11.524	30.213			
Standard of care with the addition of solriamfetol (37.5, 75, 150 mg)	[redacted]	11.969	30.213	[redacted]	0.445	[redacted]

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

There are three common placebo elements that may be considered in the context of trials (4): (i) true placebo (ii) Hawthorne effect, or (iii) regression to the mean (explained in detail in Section 2.3.2).

The original Company model assumed that the placebo effect in TONES 3 was due to the Hawthorne effect, and incorporated a 'centring' mechanism (Company Submission Form B.3.3.2) to adjust for this placebo effect, and allow only the incremental effects of solriamfetol to be assessed in the CE analyses.

The ERG stated that the placebo effect observed in TONES 3 was due to a regression to the mean and removed the centring exercise; this generated counterintuitive outcomes (e.g. where giving an active treatment clinically demonstrated as superior to placebo in TONES 3, resulted in fewer QALYs). To adjust for the implausible outcomes, the ERG added a fourth health state (for patients who discontinue solriamfetol due to adverse events but are still considered responders) to the Company's model to allow for a response to treatment in the SoC arm. Despite the addition of this fourth health state, the ERG model continued to produce counterintuitive outcomes (with 'no treatment providing more QALYs either from the start, or after a number of years, depending on the discontinuation rates per treatment).

Table 2. Summary table of original and revised assumptions in the Company's model

	Company's original base case assumption	Company's revised base case assumption	Rationale
Decision problem			
Population	Patients in the TONES 3 mITT Population with ESS >10	Patients in the TONES 3 mITT Population with ESS>12	As outlined in the Company's TE response, the Company has established that patients with ESS>12 would have the greatest clinical need and derive the greatest benefit from solriamfetol. The Committee agreed that ESS>12 should be used in the modelling.
Clinical effectiveness			
Change in ESS: Centring exercise	Changes in ESS modelled using IPD from TONES 3 'centred' to account for placebo effect	Unchanged from original base case	Additional detail for this rationale is presented in Section 2.3.2. The placebo effect in TONES 3 could be due to a (i) true placebo (ii) Hawthorne effect, (iii) regression to the mean. The Company's original model conservatively assumed this was a Hawthorne effect and conducted a centring exercise to adjust both the placebo and solriamfetol arms and allow only the incremental effect of solriamfetol to be assessed. The ERG suggested the placebo effect was due to regression to the mean and removed this centring exercise, which created implausible results in the ERG's model. The Committee was concerned about the validity of some outputs generated by the ERG's model. The Company agrees with the concerns raised by the Committee however, and as requested by the Committee, the revised Company model allows an investigation into a potential contribution of regression to the mean. The Company believes the placebo effect in TONES 3 is primarily a true placebo effect, however (as per the original model), the Company's revised model takes a conservative approach and assumes a Hawthorne effect, thus the ICERs may underestimate the true cost effectiveness of solriamfetol (further detail in Section 2.3.2).

	Company's original base case assumption	**Company's revised base case assumption**	**Rationale**
Definition of treatment response	Reduction in ESS ≥ 3	Reduction in ESS ≥ 2	Per ACD 3.8, the clinical experts said that while an ESS reduction of ≥2 points may be appropriate, there is no consensus on what can be considered a clinically relevant ESS reduction and that it varies by individual. Therefore, the revised model reflects the preferred assumption of the clinical experts and the Committee, defining response as an ESS reduction of ≥2 points.
Duration of treatment response	Responders: reduced ESS is sustained while the patient remains on solriamfetol, with ESS returning to mean baseline ESS upon discontinuation. Non-responders: ESS returns to mean baseline ESS from the point of response assessment (i.e. once a patient is determined a non-responder).	Unchanged from original base case	The ERG incorporated 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 were required to make two assumptions (i) the proportion of discontinuers who respond and, (ii) the level of response that these discontinuers achieve. As per the Company's TE response, the ERG's model's fourth health state is only necessary to account for the inconsistencies that arise from the ERG's assumption that the efficacy in the SoC 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'. The Committee was concerned about the validity of some outputs generated by the ERG's model, and the Company agrees with these concerns. The Company revised model therefore made no change to the original assumption and maintains (based on TONES 5 data) that the reduced ESS score is sustained while patients remain on solriamfetol treatment, but that ESS scores return to baseline ESS after patients discontinue solriamfetol.

	Company's original base case assumption	Company's revised base case assumption	Rationale
Loss of efficacy, adverse events and discontinuation			
Loss of efficacy	3.6% discontinuation due to loss of efficacy per year for solriamfetol (not-dose specific)	Dose-specific discontinuation due to loss of efficacy rates for solriamfetol as estimated from TONES 5 data	Solriamfetol treatment discontinuation due to loss of efficacy in TONES 3 and 5 was dose-dependent. However, the rates in the Company original model were the same across all solriamfetol doses. In the revised Company model, the loss of efficacy assumptions are as per the ERG's preferred assumptions: dose-specific discontinuation rates due to loss of efficacy were based on TONES 5. Note that TONES 5 did not assess the solriamfetol 37.5 mg dose, therefore due to an absence of data for this dose, discontinuation rates in the model for the 37.5 mg dose were assumed to be the same as those for the 75 mg dose.
Discontinuation due to TEAEs	0% in induction 3.7% per year in maintenance	Dose-specific discontinuation rates based on TONES 5 data	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. As per the ERG's preferred assumptions, the dose-dependent estimates for the maintenance phase (i.e. 12 weeks onwards) are based on TONES 5 data. Note that TONES 5 did not assess the solriamfetol 37.5 mg dose, therefore due to an absence of data for this dose, discontinuation rates for 37.5 mg were assumed to be the same as those for the 75 mg dose
Adverse event costs and disutility	GP contact for AEs resulting in discontinuation. No cost for other AEs No disutility for AEs	Unchanged from original base case	Most AEs in TONES 3 were transient and mild/moderate in severity (5) thus the cost and disutility of these AEs was not included in the model. The modelling of SAEs is described in ***The cost of hospitalisation due to SAEs***, below.

	Company's original base case assumption	Company's revised base case assumption	Rationale
Resource use and costs			
Cost of solriamfetol	[redacted] per pack of 28 x 75 mg film coated tablets (equating to a unit price [redacted] per 75 mg tablet). [redacted] per pack of 28 x 150 mg film coated tablets (equating to a unit price [redacted] per 150 mg tablet).	[redacted] per pack of 28 x 75 mg film coated tablets (equating to a unit price [redacted] per 75 mg tablet).[redacted] per pack of 28 x 150 mg film coated tablets (equating to a unit price [redacted] per 150 mg tablet).	In response to the advice received from NICE and the ERG through the appraisal consultation document (ACD), the Company made changes to the model and has now accordingly reduced the price in the revised Company model to reflect a new commercially confidential patient access scheme (PAS) price for solriamfetol.
Dose split for solriamfetol	40/40/20 split for solriamfetol 37.5 mg, 75 mg and 150 mg	[redacted] split for solriamfetol 37.5 mg, 75 mg and 150 mg	Solriamfetol is available in 37.5 mg, 75 mg and 150 mg doses, with varying cost and efficacy. CE results for these different doses were weighted (based on dose-splitting assumptions), to inform CE comparisons between solriamfetol and SoC. The dose splits for the Company base case have been amended to reflect the ERG's preferred assumption (based on [redacted]) and additional scenarios are provided in Section 2.4 for solriamfetol 37.5/75/150 mg dose splits of: • 40/40/20 split • 33/33/33 split • 20/40/40 split [redacted]; Note that both the 37.5 and 75 mg doses would be administered using the 75 mg formulation (7).

	Company's original base case assumption	Company's revised base case assumption	Rationale
The cost of hospitalisation due to SAEs	SAEs were not modelled	Cost of hospitalisation due to AEs was applied to both the solriamfetol and placebo arms using the dose-specific rates of hospitalisation due to SAEs from the TONES 3 RCT.	In the ERG model, hospitalisation costs were estimated based on rates of SAE-related hospitalisations for patients with OSA in TONES 5 (due to the TONES 5 open label, single-arm study design, all patients were treated with solriamfetol, with no control arm). The ERG calculated that in TONES 5 [redacted]% of solriamfetol-treated patients were hospitalised for SAEs. This included all events irrespective of a relationship to solriamfetol; only one SAE was deemed treatment-related in TONES 5 (n=1 stroke [redacted] in the 150 mg arm). TONES 5 data are non-comparative, single arm, open label data, and will likely bias the analysis against solriamfetol. Per the NICE methods guide, RCTs are considered to be most appropriate for measures of relative treatment effect (2), and as outlined in the Company's TE response Issue 8, Hospital Episodes Statistics data show that without exposure to solriamfetol, stroke occurs in 2.75% of the real-world OSA population per annum, and overall hospitalisation rates are [redacted] per annum. As such, had TONES 5 contained a control arm, and these patients been followed up in TONES 5, it could reasonably be expected that these patients may have experienced hospitalisations for SAEs, including stroke. For these reasons, the Company revised model applies hospitalisation rates across the solriamfetol ***and*** SoC arms using dose-specific data from the TONES 3 RCT. None of the SAEs in TONES 3 were deemed treatment related, however, the company adopted a conservative approach and assumed that all SAE-related hospital admissions in TONES 3 were deemed treatment-related. As such, hospitalisation rates are calculated from dose-specific SAEs in each arm (solriamfetol and placebo),

	Company's original base case assumption	Company's revised base case assumption	Rationale
			irrespective of a relationship to study drug; this is consistent with the approach adopted by the ERG for their analysis using TONES 5 data. As per ERG's report Section 6.1, Table 34, the model does not consider a utility reduction due to hospitalisation since its effect on QALYs is likely to be negligible.
Other model assumptions			
Time horizon	Lifetime (up to age 100 years)	Unchanged from original base case	The lifetime time horizon is assumed in the Company's and ERG's base-case analyses.

Abbreviations: AEs, adverse events; CE, cost effectiveness; ERG, evidence review group; ESS, Epworth Sleepiness Scale; GP, general practitioner; IPD, individual patient level data; mITT, modified intent-to-treat; NICE, National Institute for Health and Care Excellence; OSA, obstructive sleep apnoea; QALY, quality adjusted life year; SA, scenario analysis; SAE, serious adverse event; SoC, standard of care; TE, technical engagement; TEAEs, treatment emergent adverse events.

2. Company comments on ACD and additional analyses

Comment number	Comments *Insert each comment in a new row.* *Do not paste other tables into this table, because your comments could get lost – type directly into this table.*
1	For additional analysis in response to ACD 3.19 Clinical and cost effectiveness of solriamfetol alone compared with standard care, see Section 2.1
2	For additional analysis in response to ACD 3.6 Sensitivity analyses to assess the impact of missing data on compliance to primary therapy at baseline, see Section 2.2
3	For additional analysis in response to ACD 3.19 Sensitivity analyses to assess the potential impact of regression to the mean, see Section 2.3
4	For comment on ACD 3.11 Use of SF-6D data from the Company's trials to assess quality of life measures, see Section 2.4
5	For comment on ACD 3.14 Dose split assumptions and appropriateness of using these, see Section 2.5
6	For additional analysis in response to ACD 3.13 Hospitalisation costs for serious adverse events, see Section 2.6
7	For comment on ACD 3.4 Resource Use through requirement for more monitoring of compliance to CPAP, see Section 2.7
8	For comment on ACD 3.12 Sensitivity analysis to explore the impact of partner utilities using EQ-5D, see Section 2.8
9	For comment on ACD 3.4 Possibility that solriamfetol could be prescribed in primary care, see Section 2.9
10	Comments on other issues are provided in Section 2.10: • On the committee's statement that there is a high level of uncertainty in the analyses, and an acceptable ICER is below £20,000 per QALY gained • On restricting solriamfetol to patients with ESS > 12 in the Company base case • On the Committee's description of CPAP as a comparator for solriamfetol • On the ERG's comment that it is difficult to interpret the TONES clinical evidence demonstrating the placebo effect is unlikely regression to the mean

2.1. Comment 1. On the request for clinical and cost effectiveness analysis of solriamfetol alone compared with standard care

In the ACD, the Committee recalled that the marketing authorisation for solriamfetol includes people who may not be using a primary OSA therapy anymore. The Committee asked the Company to provide clinical and cost-effectiveness of solriamfetol alone for people who cannot tolerate CPAP. The Company believes this would include the subgroup of people with mental health or neurodegenerative conditions who may be unable to adequately use CPAP regularly (described by the clinical expert in ACD 3.17) (3).

Analysis of the TONES 3 IPD determined that 26.5% of patients in the solriamfetol arm and 30.3% of patients in the placebo arm were not using a primary OSA therapy at baseline. The remaining 73.5% and 69.7% of patients, respectively, were using a primary OSA therapy. Of the patients using a primary OSA therapy, approximately 92% were using PAP, approximately 2% were using non-PAP, and in 6%, the device was not specified. This is consistent with UK clinical practice where the majority of people using a primary OSA therapy will be receiving CPAP therapy (8). As could be expected in clinical practice, patients were using this primary OSA therapy at varying degrees of compliance, however all patients were encouraged to continue a stable level of use/non-use of their primary OSA therapy throughout the study.

The IPD for TONES 3 can therefore be categorised into (i) patients who were using a primary OSA therapy at baseline vs (ii) patients who were not using a primary OSA therapy at baseline. Note that patients in group may have been using diet and lifestyle modifications however this data was not captured in the trial therefore these data can be considered a proxy for 'solriamfetol alone for people who cannot tolerate CPAP'. Summary data for patients in TONES 3 using vs not using primary OSA therapy is presented in Table 3. While this was not a pre-specified analysis in the original study, it is of merit here to provide the necessary evidence for translation of the clinical trial data into a real-world context.

Table 3. Scenario analysis: summary data for patients using vs not using primary OSA therapy at baseline in TONES 3

	Responders (%)	Mean change in ESS from baseline	Responders (%)	Mean change in ESS from baseline
	Using primary OSA therapy		Not using primary OSA therapy	
Solriamfetol 37.5 mg	[redacted]	[redacted]	[redacted]	[redacted]
Solriamfetol 75 mg	[redacted]	[redacted]	[redacted]	[redacted]
Solriamfetol 150 mg	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: ESS, Epworth Sleepiness Scale; OSA, obstructive sleep apnoea.

The results of cost-effectiveness analyses for these subgroups of patients are presented in Table 4 and Table 5. This analysis demonstrates that solriamfetol is a cost-effective treatment choice both in patients who are receiving a primary OSA therapy and those who are not using a primary OSA therapy (for example due to CPAP intolerance, neurodegenerative conditions, or mental health conditions as described in the ACD), with both ICERs falling substantially below the acceptable £20,000 per QALY gained specified by the Committee.

Table 4. Scenario analysis: patients using a primary OSA therapy at baseline

Technologies	Total costs (£)	Total QALYs	Total LYG	Incremental costs (£)	Incremental QALYs	ICER versus baseline (£/QALY)
Standard of care without solriamfetol	£4,811	11.575	30.215			
Standard of care with the addition of solriamfetol ([redacted] 37.5, 75, 150 mg)	[redacted]	11.991	30.215	[redacted]	0.415	[redacted]

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

Table 5. Scenario analysis: patients not using a primary OSA therapy at baseline

Technologies	Total costs (£)	Total QALYs	Total LYG	Incremental costs (£)	Incremental QALYs	ICER versus baseline (£/QALY)
Standard of care without solriamfetol	£4,810	11.373	30.207			
Standard of care with the addition of solriamfetol ([redacted] 37.5, 75, 150 mg)	[redacted]	11.893	30.207	[redacted]	0.521	[redacted]

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

2.2. Comment 2. On the request for sensitivity analyses to assess the impact of missing data on adherence to primary therapy at baseline

Per ACD 3.6, the committee concluded that compliance to a primary OSA therapy like continuous positive airway pressure (CPAP) is unlikely to be affected by treatment with solriamfetol, but that more data were needed.

The Company previously presented the peer-reviewed Schweitzer 2021 manuscript that examined whether or not solriamfetol affected compliance to using primary OSA therapy (i.e. positive airway pressure [PAP], oral pressure therapy, an oral appliance, or an upper airway stimulator) in an open-label extension trial (9). These data have, therefore, been assessed by the clinical and academic sleep community and published as a valuable information resource to understand the impact of introducing solriamfetol on primary OSA therapy compliance, including PAP or CPAP compliance. Although this is a peer-reviewed manuscript, the ERG raised queries about the analyses:

- ACD 3.6 “The ERG noted that the results of these analyses were highly uncertain because of missing data and poor reporting. It said that the estimates were not reported separately for people classified as ‘compliant’ (adherent) or ‘non-compliant’ at baseline” (3).
- ERG Report Section 3.2.6.1.4 and ERG critique of company response to TE, Section 2.1 raise queries around the impact of missing data and the definition of compliant in the Schweitzer 2021 analysis (9).

The Company provide detailed information in Sections 2.2.1 and 2.2.2 to clarify that the populations used in the compliant/non-compliant analyses in Schweitzer 2021 were based on compliance levels as defined at baseline, and to address the issue of potential missing data. In addition, the Company present a new analysis using a “worst-case scenario” approach in Section 2.2.3, which demonstrates that even in the worst-case scenario, compliance to primary OSA therapy is maintained at high levels.

In conclusion, the data demonstrate that patients’ use and compliance to primary OSA therapy is unlikely to be affected by the introduction of solriamfetol for managing their residual EDS.

2.2.1. Definition of compliance/non-compliance in Schweitzer 2021

The Company clarify that the analysis is stratified by compliance levels to primary OSA therapy *at baseline.* The definition of compliance was as per the primary studies that formed the basis for the Schweitzer 2021 analysis; this same definition was used as a stratification factor in the stratified randomisation in order to minimise the potential bias described by the ERG. The definition of “compliant” vs “non-compliant” was described in the methods by Schweitzer 2021:

- “For the purpose of defining subgroups of participants who were adherent or nonadherent to OSA primary therapy at baseline, adherence was defined as device use for at least 4 hours per night on at least 70% of nights for devices with downloadable data; device use on at least 70% of nights for devices with no downloadable data; or effective surgical intervention” (9).

The definition in the primary studies (i.e. TONES 3) was:

- “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), [redacted] use of an oral appliance on ≥70% of nights (≥5 of 7 nights/week), or receipt of an effective surgical intervention for OSA symptoms”.

2.2.2. Query over missing data in Schweitzer 2021

Within the Schweitzer 2021 publication, missing data were accounted for in a standardised way (last observation carried forward); this is acknowledged in the paper as a minor limitation of the analysis (9). Furthermore, the Schweitzer 2021 publication states:

- “OSA therapy use data were summarised by percentage of nights used (from electronically retrievable and diary data), number of hours/night for those with electronically retrievable

information, and percentage of nights used more than half of the night for those who completed a diary."

Note that the data from the analysis considered as "missing" by the ERG were only considered missing due to a difference in the way that "compliance" was determined in patients using a primary OSA therapy that *did* versus *did not* collect compliance data electronically. Patients reporting use of a device for which usage data could not be retrieved electronically reported their usage and estimated the duration of use as (i) half of the night, (ii) less than half of the night or (iii) don't know. This was a pre-specified measure of compliance, and this electronic compliance data is not considered to be missing data.

2.2.3. New analysis demonstrating that data acknowledged as missing in Schweitzer 2021 have minimal impact on rates of compliance to primary OSA therapy

In addition to the substantial certainty on primary OSA therapy compliance provided in the published Schweitzer 2021 manuscript, the Company have since conducted additional sensitivity analyses to assess the impact of the small amount of missing data. Applying the most austere imputation methodology based on the CHMP Guideline on Missing Data in Confirmatory Clinical Trials (10), the Company re-evaluated the data using a worst case analysis of missing data.

A model was created where missingness[1] of data was assumed "not at random", and entirely dependent on random allocation to treatment or control arms, consistent with a worst-case scenario described by CHMP (10). Although this scenario is implausible due to the stratified randomisation of compliance, it helps to illustrate what an extreme scenario could cause in terms of primary OSA therapy compliance:

- The observed cohort had [redacted] patients with [redacted] observations. After adjustment for three baseline factors (hours of PAP use per night, percentage of nights compliant, and ESS), data were imputed as non-compliant for missing patients in the solriamfetol arm and compliant for the placebo arm. This resulted in [redacted] patients with [redacted] observations.
- In this austere model, participants compliant to primary OSA therapy at baseline and subsequently receiving solriamfetol demonstrated [redacted] hours by week 12. Compliance with PAP is generally defined as ≥4 hours on 70% of nights (11-14), and this level of compliance remains reassuringly exceeded in this pessimistic 'worst case scenario' analysis.

[1] Missingness can be defined as (i) the existence of missing data and (ii) the mechanism that explains the reason for the data being missing. The extent to which missing values lead to biased conclusions about the magnitude of any treatment effect is influenced by many factors, including the relationship between missingness, treatment assignment and outcome; the type of measure employed to quantify the treatment effect and the expected changes over time for the variables being measured.

2.2.4. Conclusion regarding concerns over missing data and definition of compliance with primary OSA therapy

In conclusion, primary OSA therapy use is unlikely to be affected by the introduction of solriamfetol. The clinical expert opinion presented in ID1065 for pitolisant agrees with the clinical expert advice collected by Jazz and presented in ID1499 for solriamfetol, that it is unlikely that pharmacotherapy will result in a reduction in compliance to primary OSA therapy (1, 3). It follows that as solriamfetol is unlikely to displace primary therapies such as CPAP for OSA, there is no onward impact on partner utilities removing the uncertainty around this topic (ACD 3.12 “The impact on partner utilities of displacing treatments such as CPAP was also uncertain.”).

Furthermore, the data in the Schweitzer peer-reviewed manuscript and the additional analysis presented here substantially exceed the depth of data presented in ID1065 for pitolisant, where based on patient and clinical expert opinion, the Committee concluded that "CPAP use is unlikely to be affected by treatment with pitolisant hydrochloride because of regular monitoring” (1).

2.3. Comment 3. On the request to assess the potential impact of regression to the mean

The Committee would have preferred some analysis assuming a regression to the mean effect. The Company has made some amendments to the model assumptions to facilitate an investigation of the impact of regression to the mean on the ICER.

The Company position is that the placebo effect observed in TONES 3 is a true placebo effect, however the Company’s revised model maintains the conservative approach that the placebo effect is due to a Hawthorne effect. Thus any ICERs presented likely underestimate the cost-effectiveness of solriamfetol.

2.3.1. Context for this analysis

The information supporting the Company’s placebo adjustment using the Hawthorne effect requires an understanding of the TONES clinical trial study designs and the different elements potentially contributing to the placebo effect. A brief summary of these is provided below:

1. TONES 3 was the pivotal randomised controlled trial for solriamfetol in treating EDS due to OSA. Patients were randomised 1:1:1:2:2 to placebo or solriamfetol 37.5, 75, 150, or (unlicensed) 300 mg respectively for the 12 week duration of the trial.
2. All patients enrolled in TONES 3 were receiving standard of care (SoC) to manage their underlying OSA. Patients fell into one of three groups:
    a. Currently using a primary OSA therapy (including positive airway pressure [PAP], oral pressure therapy, an oral appliance, or upper airway stimulator)
    b. Historically made an attempt for at least 1 month to use one or more primary OSA therapies with at least 1 documented adjustment to optimise the primary OSA therapy
    c. Had a history of a surgical intervention intended to treat OSA symptoms

3. Patients continued to use a primary OSA therapy throughout TONES 3, therefore the placebo and solriamfetol arms of the trial, respectively, can be considered to reflect 'SoC without solriamfetol' and 'SoC with the addition of solriamfetol'. This terminology is used throughout this document to describe the arms of the trial as modelled in the CE analysis.
4. In TONES 3 patients in the SoC without solriamfetol (i.e. placebo) arm achieved an improvement (i.e. reduction) in mean ESS score from baseline to week 12. Although this improvement did not reach statistical significance, it demonstrated a placebo effect in the trial.
5. Three common placebo elements may be considered in the context of clinical trials (4):
    a. True placebo effect: psychological patient expectancy that is generalisable to routine practice
    b. Hawthorne effect: psychological patient expectancy effect that is specific to the clinical trial setting (i.e. a patient's response to observation and assessment)
    c. Regression to the mean effect: arises from natural variation in the patient's condition over time, and the potential preferential selection of patients with acutely severe disease into trials; these patients are likely to show improvement when disease severity is next measured, regardless of any treatment benefit, as they tend toward their individual mean state. The extent to which the regression to the mean effect occurs in clinical practice depends on the similarities between the criteria used to select patients for treatment in practice vs those used to select patients in the trial.

6. As outlined in the Company submission and per the additional data presented in Section 2.10.4 of this document, the ***Company believes the placebo effect observed in TONES 3 was principally due to a true placebo effect.*** However, the ***Company's revised base case analysis conservatively maintains that the improvement in the placebo arm was due to the Hawthorne effect*** (4), such that patients receiving placebo reported a reduction (i.e. improvement) in ESS because they were being observed within the trial.
7. This base-case assumption is consistent with advice from the clinical experts for ID1065 for pitolisant (1), that the placebo effect observed in the pitolisant trials could be Hawthorne effect (i.e. patients reported an improvement in ESS due to more frequent contact with trial investigators than they would have with clinicians in clinical practice).
8. To account for the placebo effect, the Company performed a 'centring exercise' on the TONES 3 individual patient level data to remove the placebo effect from *both* the SoC without solriamfetol (i.e. placebo arm) and the SoC with the addition of solriamfetol groups (i.e. solriamfetol arm) in the model and allow only the incremental effects of solriamfetol to be assessed. This centring exercise was considered plausible by the Committee (3).

9. The ERG stated that the improvement in the SoC without solriamfetol arm could, at least in part, be due to a natural 'regression to the mean' effect as described in Point 5 above. The ERG assumed that the response to treatment observed in the placebo group in TONES 3 would also occur in routine clinical practice. To facilitate this assumption, the ERG were required to (ii) modify the model structure and introduce a fourth health-state (Responder No Treatment), and (ii) make a number of assumptions, including:
    a. the rate at which patients on SoC without solriamfetol discontinue treatment (or move to a non-response state)
    b. the proportion of patients on solriamfetol who discontinue yet maintain an improvement in their ESS, despite not receiving any treatment
10. In this new 'Responder No Treatment' health state, a proportion of patients who stopped solriamfetol retained an ESS response (despite not receiving active treatment for their EDS). However, this fourth health state and its supporting assumptions in the ERG model led to some implausible results (e.g. in the ERG base case, after a number of years SoC with solriamfetol gains fewer QALYs than SoC without solriamfetol [resulting in the possibility that SoC alone without solriamfetol dominates Soc with the addition of solriamfetol], and that the modelling scenario requires 'no treatment' to be discontinued and thus cannot reflect clinical practice).
11. The Committee was concerned about the validity of some outputs generated by the ERG's model, including the percentage of people in the SoC group who still have a response to treatment at 3 years and 10 years. The Committee noted that the level of response in the SoC group and the difference between the solriamfetol vs placebo groups was implausible.
12. The Committee requested that the Company explore a regression to the mean effect. The Company agrees with the concerns raised by the Committee and therefore the revised Company model retains the original three health state structure. However, the Company has amended other model assumptions to align with the Committee's preferred assumptions and used this revised model to conduct a sensitivity analysis to explore a regression to the mean effect, as requested by the Committee.

2.3.2. Company model: regression to mean sensitivity analysis

The Committee accepted that there was likely to have been some observation bias in the trial. The Committee acknowledged that there may be some regression to the mean, so there was a need to understand its potential impact by conducting sensitivity analyses (3). As requested by the Committee, the Company model has been amended to allow sensitivity analysis investigating of a potential regression to the mean in TONES 3. This new sensitivity analysis uses the raw unadjusted IPD from TONES 3 for both the SoC without solriamfetol group (i.e. placebo arm of TONES 3) and the SoC with the addition of solriamfetol group (i.e. solriamfetol arm of TONES 3).

The original Company model differentiated between responders and non-responders (i.e. those with/without sufficient reduction in ESS, respectively) in both the SoC without solriamfetol arm and SoC with solriamfetol arms. However, in the original model, the centring exercise to adjust for placebo effect meant that all of the patients in the SoC without solriamfetol (i.e. placebo) arm were considered non-responders by default, and therefore those patients remained at their baseline ESS for the lifetime of the model. In order to allow investigation of a regression to the mean, the revised Company model

removes the centring exercise and the responder and non-responder dichotomy, and instead considers the SoC without solriamfetol arm as a single group:

- As patients receiving SoC with placebo were not receiving active treatment for their residual EDS, there was no requirement to differentiate between responders and non-responders to treatment (i.e. those with or without an ESS reduction of ≥2 points). The overall mean reduction in ESS for these patients was [redacted] at week 12 of TONES 3, and in this sensitivity analysis, the patients remain at this ESS level for the lifetime of the model.
- For patients receiving SoC with the addition of solriamfetol (i.e. receiving active treatment for their residual EDS), the model assesses if patients are responders or non-responders to treatment at week 12 (i.e. those with or without a mean ESS reduction of ≥2 points, per the ERG and Committee's preferred assumption).
- In patients receiving SoC with the addition of solriamfetol who do not respond to treatment, and any patients who initially respond but subsequently discontinue due to a lack of efficacy or adverse events (AEs), their ESS upon discontinuing solriamfetol immediately changes to that of the SoC without solriamfetol group ([redacted]), reflecting the (regressed) mean position for a patient now receiving only SoC for their underlying OSA.

Table 6 presents results of the sensitivity analysis investigating a regression to the mean effect and allows the relative impact of all three placebo elements (regression to the mean, true placebo and Hawthorne effect) to be explored by providing a weighted average of the three alternative approaches. In this combined placebo effect analysis, the table displays the proportion of the placebo effect contributed by regression to the mean and true placebo, such that the remaining proportion contributed by the Hawthorne effect is calculated as:

% Hawthorne = 100% - (% true placebo + % regression to the mean)

- As outlined in the original Company submission, it **is likely** that the improvement in ESS observed in the SoC without solriamfetol arm is a true placebo effect; in addition, extensive clinical evidence is described in Section 2.10.4 of this ACD document further demonstrates the placebo effect in TONES 3 is likely a true placebo and is not regression to the mean.
- The Lincoln Medical company submission (Section 2.13.1) for NICE ID1065 for pitolisant (15) notes that a placebo effect is observed in the pitolisant trial; this is also noted in the ACD for ID1065, with the Committee concluding that it would be appropriate to explore approaches to adjust for the placebo effect in the trial (1). The Committee for ID1065 suggested that a centring exercise could be used to adjust for this [i.e. Hawthorne] effect but did not make reference to a regression to the mean effect (1).

Based on the above points, the Company maintain their position that the majority of the placebo effect in TONES 3 is a true placebo effect, therefore the ICERs in Table 6 likely underestimate the cost-effectiveness of solriamfetol and the true ICER for solriamfetol is likely in the bottom left hand portion of this table and thus below the acceptable ICER of below £20,000 per QALY gained agreed by the Committee (3).

- The top-left ICER reflects the Company's revised base case, with all of the placebo effect due to Hawthorne effect (i.e. 100% Hawthorne effect; calculated as 100% minus [0% true placebo plus 0% regression to the mean]).
- Conversely, the top-right ICER reflects a highly conservative approach, assuming 33% regression to the mean and 0% true placebo (i.e. 67% Hawthorne effect; calculated as 100% minus [0% true placebo + 33% regression to the mean]).

Table 6. Sensitivity analysis* considering alternative placebo mechanisms (ICERs)

		Regression to the mean						
		0%	5%	10%	15%	20%	30%	33%
True placebo	0%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	5%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	10%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	15%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	20%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	30%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	40%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	50%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	60%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	70%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
	80%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]		
	90%	[redacted]	[redacted]	[redacted]				
	100%	[redacted]						

Abbreviations: ICER, incremental cost effectiveness ratio.
*Analysis assumes a dose split of [redacted] for solriamfetol 37.5/75/150 mg.
Grey cells indicate implausible scenarios that exceed the maximum 100%.

2.4. Comment 4. On the request to use SF-6D data from the Company's trials to assess quality of life measures

It is recognised that there is considerable need for a well validated and sufficiently responsive quality of life measure for evaluating people with sleep disorders (16). The EQ-5D and SF-6D questionnaires are both generic measures to ascertain health status and neither questionnaire includes a sleep domain nor a dimension to specifically capture the impact of EDS on quality of life in people with OSA.

The committee wanted to see the SF-6D in the analysis and concluded that mapping from the ESS to the EQ-5D may not adequately capture changes in quality of life. However, neither the EQ-5D nor the SF-36 data collected in the TONES trials reflected the substantial burden of OSA on QoL. Despite the high burden of illness in patients with such a disabling symptom, the baseline utility scores collected in the trials were inconsistent with the widely accepted negative impact of EDS and OSA. The reasons why

these health questionnaires were incapable of capturing changes in QoL in the trials are discussed at length in the Company submission Form B and Technical Engagement response (e.g. a lack of a sleep domain, inability to capture impact on relationships, high baseline utility scores, patient adaptation to sleepiness over time).

Furthermore, as acknowledged by the ERG, the 12-week trial duration was likely insufficient to capture the effect of solriamfetol treatment on quality of life. Whilst there is an immediate improvement via the vitality domain of SF-36, this domain contributes relatively little to the overall utility scoring compared to domains which are likely to take longer for a patient to achieve a substantial change in score or reach their 'new normal' (i.e. physical functioning, physical role limitations, general health perceptions).

Although the populations in the trials are similar to the UK population (17), country-specific differences in driving restrictions may have influenced quality of life. In the UK, the DVLA prevent patients with EDS and OSA from driving (18), thus the Company did not include the influence of road traffic accidents in their cost effectiveness analysis. However most patients were recruited from the United States where patients could continue driving despite their EDS. Driving has been identified as an important instrumental activity of daily living, and a systematic review of driving cessation showed that loss of driving ability was associated with substantially reduced quality of life in adults of similar age to the trial population (19). Therefore the impact on QoL in a US based population is unlikely to reflect the impact of improved EDS in a UK/EU cohort.

During the appraisal of ID1065, the pitolisant ERG suggested that SF-6D may be more sensitive than EQ-5D in capturing QoL benefits (1). The pitolisant company provided a scenario that mapped ESS scores to SF-6D. The Committee for ID1065 agreed that the pitolisant company's scenario using SF-6D might be preferable, but stated that more understanding was needed to determine how well mapping to SF-6D captures quality-of-life benefits (1). The Committee for ID1065 concluded that it preferred the EQ-5D utility values derived from the clinical trials and that more detailed evidence should be provided to explain why EQ-5D is insensitive to capturing changes in a person's quality of life (1). Therefore, in the absence of appropriate HRQoL trial data, the Company maintain that the best method for describing the QoL improvement for patients with OSA is the use of the EQ-5D from the NHWS mapping formula in the base case, with an analysis using the McDaid algorithm provided in a scenario. Furthermore, it is likely that both generic measures underestimate the true relationship between ESS and utility. If the utilities from the time trade off study represent what this might look like in a real world setting, it suggests that the true ICERs for standard of care with the addition of solriamfetol vs standard of care without solriamfetol may be much lower than presented in this document.

Following the ACD, the Company discussed with clinicians the topic of using health questionnaires to measure changes in QoL associated with changes in EDS (20). Based on these discussions, the Company's resolve in the use of the mapping approach was strengthened. Clinicians described a very substantial burden on QoL for patients with EDS. Note that these clinicians primarily specialised in narcolepsy but agreed that their responses could also be used to describe QoL for EDS due to OSA. In general, clinicians agreed with the shape of the NHWS and McDaid graphs, confirming they expected to see a correlating decrease in QoL as a patient's sleepiness increased. Clinicians highlighted that these are generic scales and not tailored for EDS, and the clinicians felt that these generic scales

underestimate the true burden of EDS on QoL, thus the QALY gain with solriamfetol is likely an underestimate, as supported by the scenario using the time trade off study utility values.

2.5. Comment 5. On the conclusion that the range of dose split assumptions included in the company's and ERG's analysis is appropriateness

In all clinician interviews (both conducted prior to the submission and conducted post-ACD), clinicians consistently reported that the dose split would be determined by response rate, and that prescribers aim for the lowest effective dose (21). Due to the absence of pharmacotherapies licensed and indicated for the management of EDS due to OSA at the time of writing (24 June 2021), UK clinicians were unable to describe what the final dose split of solriamfetol 37.5, 75 and 150 mg may be in practice, but parallels can be drawn from clinicians' experience of prescribing drug therapy in narcolepsy.

KOLs with experience in the use of wake promoting agents for managing EDS due to narcolepsy (21):

- describe taking a cautious approach to titration, often with longer intervals than occurred in the trial
- use descriptions including "start low" and "slow titration" to describe dosing

At the time of the original company submission, early prescribing patterns from the US indicated a [redacted] dose split for the 37.5 mg/75 mg/150 mg solriamfetol doses, respectively. However, it is anticipated that UK prescribers will be more conservative than those of the US, and based on the anticipated UK prescribing approaches, the original base case assumed a dose split of 40/40/20. This may be considered a conservative approach given that in TONES 3 approximately 52% of patients on the 37.5 mg dose achieved normal ESS scores (ESS ≤10) by week 12 (22). It is expected that if a patient normalises on a given dose in clinical practice, that patient will remain on that dose (and would not unnecessarily titrate to a higher dose), thus in clinical practice half of patients may not titrate beyond the 37.5 mg dose.

The anticipated prescribing patterns in the UK are consistent with early prescribing data from [redacted] (6). Note that as one 75 mg tablet can be split into two x 37.5 mg daily doses (7), a pack of 28 x 75 mg tablets will last twice as long for patients prescribed the lower 37.5 mg dose.

Based on the above, it is anticipated that clinicians in the UK will slowly titrate solriamfetol starting at the lowest dose (37.5 mg) and the Company maintains that the standard approach in the UK would see the lowest available dose prescribed to the majority of patients. Although NICE and the ERG preference of a [redacted] dose split potentially sees too many patients titrating beyond the 37.5 mg dose, it is not inconsistent with the view that a low proportion of patients would receive the highest dose. Therefore, to align with the NICE & ERG preference the Company revised base case is set to a [redacted] dose split.

However, the Company note per the ACD that "The Committee concluded that the range of dose split assumptions included in the Company's and ERG's analysis is appropriate to account for the variability in clinical practice."

Therefore, the Company have provided all other dose split scenarios below (40/40/20, 33/33/33, and 20/40/40) with an investigation of the regression to the mean effect, as requested by the Committee, presented for each dose split analysis.

- Revised base-case results using [redacted] are presented in Section 2.5.1.
- Dose split scenarios are presented in Sections 2.5.2, 2.5.3, and 2.5.4

2.5.1. Revised base case results, dose split [redacted] for solriamfetol 37.5/75/150 mg

Table 7. 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	£4,810	11.524	30.213			
Standard of care with the addition of solriamfetol ([redacted] 37.5, 75, 150 mg)	[redacted]	11.969	30.213	[redacted]	0.445	[redacted]

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

Table 8. 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	£4,792	11.480	30.033			
Standard of care with the addition of solriamfetol ([redacted] 37.5, 75, 150 mg)	[redacted]	11.923	30.033	[redacted]	0.443	[redacted]

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

2.5.2. Dose split: 40/40/20 for solriamfetol 37.5/75/150 mg

Table 9. Dose split 40/40/20: revised base case

Technologies	Total costs (£)	Total QALYs	Total LYG	Incremental costs (£)	Incremental QALYs	ICER versus baseline (£/QALY)
Standard of care without solriamfetol	£4,810	11.524	30.213			
Standard of care with the addition of solriamfetol (40/40/20 37.5, 75, 150 mg)	[redacted]	11.935	30.213	[redacted]	0.411	[redacted]

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

Table 10. Dose split 40/40/20: observation bias analysis (ICERs)

		Regression to the mean						
		0%	5%	10%	15%	20%	30%	33%
True placebo	0%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	5%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	10%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	15%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	20%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	30%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	40%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	50%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	60%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	70%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
	80%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]		
	90%	[redacted]	[redacted]	[redacted]				
	100%	[redacted]						

Abbreviations: ICER, incremental cost effectiveness ratio.
Grey cells indicate implausible scenarios that exceed the maximum 100%.

2.5.3. Dose split: 33/33/33 for solriamfetol 37.5/75/150 mg

Table 11. Dose split 33/33/33: Revised base case

Technologies	Total costs (£)	Total QALYs	Total LYG	Incremental costs (£)	Incremental QALYs	ICER versus baseline (£/QALY)
Standard of care without solriamfetol	£4,810	11.524	30.213			
Standard of care with the addition of solriamfetol (33/33/33 37.5, 75, 150 mg)	[redacted]	11.988	30.213	[redacted]	0.464	[redacted]

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

Table 12, Dose split 33/33/33: observation bias analysis (ICERs)

		Regression to the mean						
		0%	5%	10%	15%	20%	30%	33%
True placebo	0%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	5%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	10%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	15%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	20%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	30%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	40%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	50%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	60%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	70%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
	80%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]		
	90%	[redacted]	[redacted]	[redacted]				
	100%	[redacted]						

Abbreviations: ICER, incremental cost effectiveness ratio.
Grey cells indicate implausible scenarios that exceed the maximum 100%.

2.5.4. Dose split: 20/40/40 for solriamfetol 37.5/75/150 mg

Table 13. Dose split 20/40/40: Revised base case results

Technologies	Total costs (£)	Total QALYs	Total LYG	Incremental costs (£)	Incremental QALYs	ICER versus baseline (£/QALY)
Standard of care without solriamfetol	£4,810	11.524	30.213			
Standard of care with the addition of solriamfetol (20/40/40 37.5, 75, 150 mg)	[redacted]	12.025	30.213	[redacted]	0.501	[redacted]

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

Table 14, Dose split 20/40/40: Observation bias analysis (ICERs)

		Regression to the mean						
		0%	5%	10%	15%	20%	30%	33%
True placebo	0%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	5%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	10%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	15%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	20%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	30%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	40%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	50%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	60%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	70%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
	80%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]		
	90%	[redacted]	[redacted]	[redacted]				
	100%	[redacted]						

Abbreviations: ICER, incremental cost effectiveness ratio.
Grey cells indicate implausible scenarios that exceed the maximum 100%.

2.6. Comment 6. On the request to include hospitalisation costs for serious adverse events in the modelling

The Company welcome the consideration of the impact on hospitalisation rates of introducing solriamfetol into clinical practice and understand that the proposed use of the gross SAE-related hospital admission rate in TONES 5 by the ERG is a proxy for hospitalisations experienced in this population.

In the ERG model, hospitalisation costs were estimated based on rates of SAE-related hospital admissions for patients with OSA in TONES 5. The ERG calculated that in TONES 5 [redacted]% ([redacted]) of solriamfetol-treated patients were hospitalised for SAEs. This included all events irrespective of a clear relationship to solriamfetol; only one such event was deemed treatment-related in TONES 5 (n=1 stroke [redacted] in the 150 mg arm). TONES 5 was a single arm, open label extension study, the data do not demonstrate *a difference* between the intervention (solriamfetol) and comparator (placebo), but instead only an absolute rate for solriamfetol and therefore the ERG analysis is limited by the assumption that all hospitalisations observed in TONES 5 would be incremental to SoC.

This approach biases against solriamfetol in cost-effectiveness analyses and the Company are mindful that this is not consistent with NICE methodology, where it is the relevant cost *differences* between the intervention and comparator that need to be considered (2). Further, the NICE methods guide states RCTs are considered to be most appropriate for measures of relative treatment effect (2). As TONES 5 was a single arm, open label extension study, the data do not demonstrate *a difference* between the intervention (solriamfetol) and comparator (placebo), but instead only an absolute rate for solriamfetol.

In the time since technical engagement and the NICE Committee meeting, the first Periodic Safety Update Report for solriamfetol has been considered by the EMA. The report spans [redacted] person-months ([redacted] person-months post authorisation) and considers that the number of adverse drug reactions in patients treated with solriamfetol in clinical practice is “relatively low”, which indicates that using the single-arm TONES 5 data in isolation likely over-estimates hospitalisation costs for this population. This further reinforces the robustness of the low AE rates for solriamfetol (including SAE and hospitalisation rates) observed in TONES 3, where it was compared with placebo.

Furthermore, as outlined in the Company’s TE response Issue 8, Hospital Episodes Statistics (HES) data show that without exposure to solriamfetol in the real-world OSA population, hospitalisation rates overall are [redacted]% per annum (for reasons other than sleep disorder), and hospitalisation for stroke – the only SAE deemed to be treatment-related in TONES 5 – occurs in [redacted]% per annum. As such, if TONES 5 had contained a control arm, it could be reasonably expected that these patients may also have experienced hospitalisations for adverse events, including stroke.

In order to maintain consistency with NICE methods to model comparative effects and to negate the limitations associated with using single-arm TONES 5 data, the Company revised base-case applies hospitalisation rates across the solriamfetol ***and*** SoC arms, based on annualised data from TONES 3. Rates are calculated from all SAEs which led to hospitalisation in each trial arm (solriamfetol; placebo), irrespective of a relationship to study drug, consistent with the approach adopted by the ERG for the ERG’s analysis of TONES 5 solriamfetol data. Data utilised are presented in Table 15; as TONES 3 was a 12-week study, observed rates are converted to an annualised rate and applied on every model cycle. Note that the Company’s revised base-case results are provided in Table 1.

Table 15: SAE-related hospitalisation from TONES 3 and applied in Company revised base-case

Intervention	n/N	Rate, % Week 12	Rate, % annualised
SoC (placebo)	[redacted]	[redacted]	[redacted]
Solriamfetol 37.5 mg	[redacted]	[redacted]	[redacted]
Solriamfetol 75 mg	[redacted]	[redacted]	[redacted]
Solriamfetol 150 mg	[redacted]	[redacted]	[redacted]

Source: TONES 3 CSR Listing 14.3.16. Note that 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.

As mentioned above, TONES 5 was a single arm, open label extension study, and as such, the data do not demonstrate *a difference* between the intervention (solriamfetol) and comparator (placebo), but instead only provide an absolute rate for solriamfetol. Therefore as per the NICE methods guide (2), the Company position is that the model should use the comparative, dose-specific data from the TONES 3 RCT.

However to allow investigation into the impact of SAEs, the Company also provide new scenario analyses accounting for the following:

- Section 2.6.1: any SAE-related hospitalisation for solriamfetol from TONES 5 vs zero rate for SoC (ERG preferred assumptions)
  - In this scenario, TONES 5 SAE-related hospitalisation irrespective of relationship to study drug is modelled, as per ERG assumptions
    - ◊ [redacted]% in the solriamfetol 150 mg arm, zero in other solriamfetol arms from TONES 5
    - ◊ Zero rate applied in the SoC arm

- Section 2.6.2: any SAE-related hospitalisation for solriamfetol from TONES 5 vs HES rate for SoC
  - In the absence of data for SoC from the single-arm TONES 5 study, English HES data is modelled showing that [redacted]% of patients with OSA receiving SoC will be hospitalised per year *for reasons other than a sleep disorder*
    - ◊ [redacted]% in the solriamfetol 150 mg arm, zero in other solriamfetol arms from TONES 5
    - ◊ [redacted]% from HES in the SoC arm

- Section 2.6.3: treatment-related SAE-related hospitalisation for solriamfetol from TONES 5 vs zero rate for SoC
  - In this scenario, the Company include only treatment-related SAEs leading to hospitalisation from TONES 5, which only included a single case of stroke in the solriamfetol 150 mg arm. This scenario may provide a more appropriate indication of incremental hospitalisation with solriamfetol over SoC than the ERG's preferred analysis. However, it should also be noted that hospitalisation for stroke is observed in the OSA population, as already highlighted above by the HES data.
    - ◊ [redacted]% in the solriamfetol 150 mg arm, zero in other solriamfetol arms from TONES 5
    - ◊ Zero rate applied in the SoC arm

2.6.1. Scenario analysis: ERG preferred assumptions for modelling hospitalisation costs

Table 16. Scenario analysis: any SAE related hospitalisation for solriamfetol from TONES 5 vs zero rate for SoC (ERG preferred assumptions)

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 ([redacted] 37.5, 75, 150 mg)	[redacted]	11.969	30.213	[redacted]	0.445	[redacted]

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

2.6.2. Scenario analysis: any SAE-related hospitalisation for solriamfetol vs HES rates for SoC

Scenario results are presented in Table 17. Despite the TONES 5 data showing fewer hospitalisations than found in a broadly matched population in HES (Patients with OSA), the Company have no evidence to suggest that solriamfetol is associated with a protective effect against hospitalisation, therefore this scenario is highly unlikely.

Table 17. Scenario analysis: any SAE-related hospitalisation for solriamfetol from TONES 5 vs HES rates for SoC

Technologies	Total costs (£)	Total QALYs	Total LYG	Incremental costs (£)	Incremental QALYs	ICER versus baseline (£/QALY)
Standard of care without solriamfetol	£8,884	11.524	30.213			
Standard of care with the addition of solriamfetol ([redacted] 37.5, 75, 150 mg)	[redacted]	11.969	30.213	[redacted]	0.445	[redacted]

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

2.6.3. Scenario analysis: treatment related SAE-related hospital admission rates for solriamfetol vs HES rates for SoC

Results are presented in Table 18.

Table 18. Scenario analysis: treatment-related SAE-related hospitalisation for solriamfetol from TONES 5 vs zero rate for SoC

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 ([redacted] 37.5, 75, 150 mg)	[redacted]	11.969	30.213	[redacted]	0.445	[redacted]

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

2.7. Comment 7. On the potential increased resource use through a requirement for more monitoring of adherence to CPAP as noted by the clinical experts

In the ACD, the clinical experts noted that if solriamfetol were recommended, the likely requirement for more monitoring of adherence to CPAP could put pressure on services; the experts said that in most sleep clinics CPAP can be monitored remotely and acknowledged that although people having solriamfetol alongside a primary therapy such as CPAP would have their use monitored (i.e. within routine practice), it may have to be more frequent. The committee concluded that adherence to a primary therapy like CPAP is unlikely to be affected by treatment with solriamfetol, but more data are needed (3).

The Company have considered this issue and provide additional information below to reassure the Committee that the introduction of solriamfetol will not put additional pressure on services. This additional evidence draws on the 2021 draft NICE guideline on obstructive sleep apnoea/hypopnoea syndrome (OSAHS), and its associated evidence reviews which help to address the proposed uncertainties surrounding the current treatment pathway, standards, and resource use for managing OSA, particularly in patients with persistent symptoms despite CPAP (23-25):

- According to the evidence reviews supporting the development of these new guidelines, the "outcomes that matter most" in OSAHS include sleepiness scores (e.g. ESS) and systolic blood pressure for hypertension (24-26), and these outcomes are therefore important in the follow-up of patients with OSA.
- In Evidence Review M the guideline committee noted that CPAP is just one aspect of the treatment for OSAHS, and that monitoring should be tailored to the person's overall treatment plan, which may include lifestyle changes and weight management, modifying sedative drugs and alcohol, stopping smoking, and treating underlying lung disease and other comorbidities. Additionally,

Evidence Review M states that although control of symptoms is important, the committee agreed that treatment efficacy cannot be decided on improvements of symptoms alone as they are an imprecise indicator of treatment success (24).

- Evidence Review N states that in current practice educational information is typically provided at an outpatient appointment 1 month after CPAP initiation and per annum thereafter, but that these appointments are not exclusively for providing education and support; e.g. during the appointment the sleep specialist would explore whether people with OSAHS have adequate control of their symptoms and whether further assistance is required to improve symptoms (25). The guideline committee agreed that providing education and support (i.e. to improve primary OSA therapy use) was reasonable as it can improve adherence and contribute to the cost-effectiveness of the intervention (25). Note that this is current practice for people newly provided with CPAP.
- The draft guidelines recommend that patients with OSAHS are assessed for adequate control of symptoms at routine follow-up (according to the person's needs), and that annual follow-up should be considered once CPAP has been optimised (23).
- In addition, the draft guidelines recommend that patients receiving CPAP for their underlying OSA receive telemonitoring (24). Telemedicine has been demonstrated to improve PAP compliance in patients with moderate to severe OSA (27), and in patients with OSA with high cardiovascular risk, telemonitoring is demonstrated to improve PAP compliance and patient-centred outcomes (28).

As outlined in the solriamfetol summary of product characteristics (SmPC), the only monitoring requirements for solriamfetol are heart rate assessment and blood pressure measurement at treatment initiation, and periodic monitoring (7). These requirements are aligned with the proposed monitoring recommended within routine standard of care for OSA described in the draft NICE guideline (23).

The Company sought the opinion of a range of clinicians practicing in England who describe a patient-centred approach to managing OSA, often with routine follow-up at approximately annual intervals. These experts suggest that patients with residual EDS may be followed up more frequently, consistent with the subsequently produced draft NICE guideline. Although it has been suggested that patients with residual EDS may be seen more regularly, as solriamfetol has been clinically demonstrated to reduce EDS in patients with OSA (5, 29), it is likely that its introduction into UK clinical practice may therefore reduce the overall burden of follow-up in this patient population.

The development of the draft NICE guideline for OSAHS is independent of the ID1499 for solriamfetol and the guidelines are representative of monitoring of underlying OSA and primary OSA therapy by specialist teams. Once/if approved, these guidelines will form routine standard of care in the UK and would be applied in the management of OSA independently of solriamfetol prescribing. In following the recommendations in the guideline, patients with OSA using solriamfetol are **unlikely** to require additional resource use compared with patients who are not receiving solriamfetol, because all patients with OSA (regardless of solriamfetol use) will have their use of primary OSA therapy routinely monitored. Based on the above, the Company feel that the introduction of solriamfetol is unlikely to require any additional resource compared with current standard of care and future standard of care proposed in the draft NICE guideline for OSAHS.

2.8. Comment 8. On the request for sensitivity analysis to explore the impact of partner utilities using EQ-5D

Following the ACD, the Company discussed with clinicians the impact of EDS on partner QoL. From these discussions, the Company understand that there can be a significant impact on the partner. This impact on the partner was acknowledged in the ACDs for both ID1499 for solriamfetol in OSA and ID1065 for pitolisant (1, 3), and the Committee for ID1499 for solriamfetol in OSA concluded that partner utility values are important to consider (3).

The impact of EDS on the partner of patients with OSA was described in Company submission Form B1.3, and Jazz completed an additional time trade-off study to demonstrate the benefit to the partner of treating the patients EDS. Given the acknowledgement by the Committee that the impact on partner utilities is important, the Company has repeated the original sensitivity analyses for the inclusion of partner utilities using the revised Company model. In these analyses, the patient utility values are mapped to create partner utility values using the time trade off study algorithm (described in Company Submission Form B.3.4.4.3). Results are presented in Table 19, Table 20 and Table 21.

These data are presented so that the Committee can see the impact of including partner utilities on the ICER. However, as the Committee believed that the time trade off study provided insufficient evidence to warrant inclusion in the modelling, the company has excluded this QALY gain due to improvements in partner utility from the revised base case (note that partner utilities were previously excluded from the original company base case, and were presented as scenario analyses only).

Given the above, the exclusion of partner utilities from the total QALY gain with solriamfetol represents a conservative approach and therefore the ICERs presented for the base case analysis would likely underestimate the cost-effectiveness of solriamfetol in managing EDS. It is unclear why the Committee believes the time trade off study provides insufficient evidence to warrant inclusion in the modelling. Unfortunately, at this stage of the STA process, the Company have insufficient time with which to carry out an additional study using an alternatively methodology (e.g. EQ-5D) that may provide more robust evidence on the impact of EDS on the partner.

Table 19. Scenario analysis: NHWS mapping patient utilities combined with partner utilities

Technologies	Total costs (£)	Total QALYs	LYG	Incremental costs (£)	Incremental QALYs	Incremental ICER
Standard of care without solriamfetol	£4,810	20.605	30.213			
Standard of care with the addition of solriamfetol ([redacted] 37.5, 75, 150 mg)	[redacted]	**21.214**	**30.213**	[redacted]	**0.609**	[redacted]

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

Table 20. Scenario analysis: McDaid mapping patient utilities combined with partner utilities

Technologies	Total costs (£)	Total QALYs	LYG	Incremental costs (£)	Incremental QALYs	Incremental ICER
Standard of care without solriamfetol	£4,810	23.943	30.213			
Standard of care with the addition of solriamfetol ([redacted] 37.5, 75, 150 mg)	[redacted]	**24.467**	**30.213**	[redacted]	**0.524**	[redacted]

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

Table 21. Scenario analysis: time trade off patient utilities combined with partner utilities

Technologies	Total costs (£)	Total QALYs	LYG	Incremental costs (£)	Incremental QALYs	Incremental ICER
Standard of care without solriamfetol	£4,810	21.296	30.213			
Standard of care with the addition of solriamfetol ([redacted] 37.5, 75, 150 mg)	[redacted]	**22.599**	**30.213**	[redacted]	**1.303**	[redacted]

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

2.9. Comment 9. On the conclusion that solriamfetol treatment is likely to be limited to secondary care but more information is needed

The committee concluded that solriamfetol treatment is likely to be limited to secondary care, but more information is needed (3). The summary of product characteristics for solriamfetol state that treatment with solriamfetol requires specialist initiation (7). Further, it is common for patients with OSA to remain within secondary and sometimes tertiary care, given the nature of the disease. In addition, as a newly licensed medication, solriamfetol carries a black triangle, severely limiting (in many cases precluding) its use in primary care at this time. The restriction of solriamfetol to secondary care is consistent with the anticipated prescribing of pitolisant hydrochloride in secondary care per the ACD for NICE ID1065 (1).

Discussions with NHS stakeholders (clinicians and pharmacists) revealed the preferred route for continuation of prescribing of solriamfetol is outsourced outpatient pharmacy from secondary care; some areas will prefer to adopt NHS contracted homecare medicines services. Dr Sonya Craig's clinical expert statement, representing the British Thoracic Society, stated "It is very unlikely that primary care would be willing to take on prescribing of this drug" (17).

NHSE Specialist Pharmacy Service has published clear principles on routes of supply for medicines to outpatients, ratified by the Regional Medicines Optimisation Committee (RMOC) (30). The document uses sodium oxybate (a medication used by sleep services) as an example of a drug that is suitable for Outsourced Outpatient Dispensing (OOPD) or Homecare Delivery for continuation of prescribing to outpatients. During the COVID-19 pandemic, many OOPD services have been couriering drugs to patients. In discussions with NHS customers, these routes have been validated as well-suited for solriamfetol. In addition, solriamfetol is listed as a restricted 'Red' drug in formularies, meaning its prescription is limited to hospital only (31-34).

In alignment with its secondary care prescribing, Jazz has listed the price of solriamfetol in the BNF and on DM&D as 'hospital only' (35).

2.10. Comment 10. Other issues

2.10.1. On the committee's statement that there is a high level of uncertainty in the analyses, and an acceptable ICER is below £20,000 per QALY gained

In ACD 3.15, the Committee felt that was a high level of uncertainty around the ICERs, in particular:

- the effect of solriamfetol on adherence to primary obstructive sleep apnoea therapy
- whether changes in quality of life were adequately captured by mapping the ESS to the EQ-5D
- the adjustment for the placebo effect
- the dose splits that will be used in clinical practice

In order to increase the certainty surrounding the ICERs presented, and in particular the issues listed above, the Company has now provided comment or additional analyses in their response to ACD. The extensive clinical evidence demonstrating the placebo effect is not a regression to the mean (Section 2.10.4), in combination with sensitivity analyses on adherence to primary OSA therapy (Section 2.1), new analyses on the cost-effectiveness of solriamfetol in patients who are CPAP intolerant (Section 2.1), new dose split analyses (Section 2.4) indicate that solriamfetol is a cost-effective treatment for managing EDS due to OSA at the lower threshold of £20,000.

The Company feels given the increased certainty surrounding these issues through the additional data and responses provided in the Company's ACD response, a threshold higher than £20,000 per QALY gained could be acceptable. The introduction of the new solriamfetol PAS price substantially reduces the ICERs to below the proposed acceptable threshold of £20,000 per QALY gained in the base case, and are therefore reassuringly cost-effective if considering thresholds higher than £20,000 per QALY.

The results of an updated probabilistic sensitivity analysis (PSA) based on the Company's revised model are presented below. The probability that solriamfetol would be the most cost-effective treatment was 75% at a threshold of £20,000 per QALY, and was 99% at a threshold of £30,000 per QALY (Figure 1). Across 5,000 PSA simulations, solriamfetol was associated with a mean cost of £[redacted] (95% CI: [redacted]) and mean total QALYs of 12.398 (95% CI: 12.387, 12.408) (Table 22). These results are

highly congruent with the deterministic results. Overall, the results remain consistent with the base case analysis.

Figure 1. Cost-effectiveness acceptability curve

Abbreviations: SoC, standard of care.

Table 22. Probabilistic sensitivity analysis results

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER incremental (£/QALY)
Standard of care without solriamfetol	£4,873 (£4,782 - £4,964)	11.866 (11.855 - 11.877)			
Standard of care with the addition of solriamfetol (37.5, 75, 150 mg)		12.398 (12.387 - 12.408)		0.531	

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

2.10.2. On restricting solriamfetol to patients with ESS > 12 in the Company base case

Section 3 of the ACD states: “It agreed that a subgroup of people with a baseline Epworth Sleepiness Scale (ESS) score of 12 should be used in the modelling (see technical report issue 2).” The discussion that took place in the Committee meeting resulted in agreement that the baseline ESS that should be used in the modelling is ESS >12. A follow-on discussion between NICE and the Company on 19 April 2021 confirmed that the baseline ESS of >12 should be used in the modelling. This amendment is reflected in the Company’s revised model and CE analyses.

2.10.3. On the Committee's description of CPAP as a comparator for solriamfetol

ACD 3.2 states "3.2 The Committee concluded CPAP is an appropriate comparator, but some people cannot tolerate it." This is contradictory to the rest of the ACD discussion where the comparison is described as (i) CPAP plus solriamfetol vs (ii) CPAP plus no additional intervention. Further, section 3.3 of the ACD states "The Committee concluded that the clinical and cost-effectiveness evidence submitted by the Company does not cover the full marketing authorisation." Here the comparison is now described as (i) no use of CPAP plus solriamfetol only vs (ii) no use of CPAP plus no additional intervention. Thus, the statement "The Committee concluded CPAP is an appropriate comparator" is contradictory. Note that the Company has provided new analysis in Section 2.1 of this ACD response, which demonstrate that solriamfetol is cost-effective both for the patients using vs not using a primary OSA therapy.

2.10.4. On the ERG's comment that it is difficult to interpret the TONES clinical evidence demonstrating the placebo effect is unlikely regression to the mean

In the ERG Response to TE Issue 4, Section 2.4, the ERG stated "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".

The data referred to by the ERG were important clinical evidence demonstrating that regression to the mean was not responsible for the placebo effect observed in TONES 3. Therefore, these clinical data from patients with OSA who were enrolled in TONES 3 or TONES 4 and then subsequently enrolled in TONES 5 have been re-examined and a new explanation of the data is provided in the below sections.

This extensive examination of clinical data provides strong evidence that the placebo effect observed in TONES 3 is not regression to the mean, consistent with comments by the ERG, clinical experts and Committee (3, 17):

- ERG report section 4.2.6.2 states "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."
- ACD 3.9 states "The clinical experts advised that a placebo effect is common in trials in this disease area and suggested it could have occurred in the TONES 3 placebo with standard care group".

2.10.4.1. Summary of trial design for TONES 3, TONES 4 and TONES 5

1. TONES 3 was the pivotal 12-week placebo-controlled randomised controlled trial for solriamfetol in treating EDS due to OSA (Section 2.3.1).
2. TONES 4 (n=122) was a 6-week study of solriamfetol for patients with OSA, comprised of a 2-week titration phase (all patients undertake solriamfetol titration), 2-week stable dose phase (all patients receive stable dose solriamfetol), and 2-week double-blind randomised withdrawal phase (patients randomised 1:1 to receive placebo or continue stable dose solriamfetol).

3. TONES 5 was an open label extension study that enrolled patients who had previously completed another TONES study. These patients can be categorised into two groups:
    a. Patients with OSA who had completed a prior TONES study (i.e. TONES 3) and immediately enrolled into TONES 5 (n=333)
    b. Patients with OSA who had completed a prior TONES study (i.e. TONES 4) but had a break in solriamfetol treatment of varying durations before enrolling into TONES 5 (n=84)

2.10.4.2. Clarification of the description of TONES 5 trial in ACD 3.9

ACD 3.9 states: "During TE, the Company presented evidence to suggest there was no regression to the mean. This included evidence from people transitioning from TONES 3 to TONES 5, a 52-week open-label trial assessing solriamfetol's long-term effectiveness. It included a 2-week placebo-controlled randomised withdrawal phase for patients moving from other TONES trials into TONES 5."

This statement requires clarification: *all of the patients* in TONES 5 had completed a prior TONES study and therefore the randomised withdrawal phase was not restricted to any specific subgroup of patients.

Further, note that patients who completed the 12-week TONES 3 study *immediately* enrolled into TONES 5 thus continued solriamfetol for only 40 weeks in TONES 5 (i.e. for a total of 52 weeks). This differs from patients who had completed a prior TONES study and had a break in treatment prior to TONES 5 who were required to complete 52 weeks of treatment within TONES 5 (29).

2.10.4.3. Evidence from patients completing TONES 3 and subsequently enrolling in TONES 5 indicates that the placebo effect is more likely to be true placebo than regression to the mean

A total of [redacted] patients with OSA who completed TONES 3, immediately enrolled in TONES 5; the ESS scores for these patients transitioning between the trials provides evidence against a regression to the mean (Figure 2).

- Patients in TONES 3 who were randomised to solriamfetol (orange line) achieved substantial improvements (i.e. reduction) in mean ESS. When these patients moved into the open label and unblinded TONES 5 trial, their ESS score further improved (i.e. reduced).
- Patients who were randomised to placebo (blue line) had improvements (i.e. reduction) in mean ESS at a smaller level compared with solriamfetol, but when these patients moved into the open label and unblinded TONES 5, they achieved rapid improvements (i.e. reduction) in ESS.
- The trend line for ESS reduction upon starting solriamfetol treatment in both TONES 3 and TONES 5 as shown in Figure 2 is highly similar, and furthermore is similar to that observed for patients both upon starting solriamfetol in TONES 4, and restarting solriamfetol upon enrolling into TONES 5 (discussed in detail in 2.10.4.4 and shown in Figure 3).
- The additional improvements (i.e. reduction) of ESS scores when patients are receiving unblinded compared with blinded solriamfetol treatment is further evidence that the effect observed in the placebo arm is not a regression to the mean. If this were a regression to the mean, the ESS scores would trend towards a reduction (i.e. improvement) in ESS value over time, however this slow

improvement in ESS after week 1 in TONES 3 is observed at a similar rate in both the placebo and solriamfetol arms, indicating this is not a regression to the mean.

Figure 2. ESS scores for patients with OSA who completed TONES 3 and subsequently enrolled into TONES 5

* All patients in TONES 5 received solriamfetol 75, 150 or (unlicensed) 300 mg; Investigators were instructed to titrate subjects to the maximal dose of solriamfetol that was tolerated to maximise therapeutic efficacy.

2.10.4.4. Evidence based on patients moving from TONES 4 into TONES 5 demonstrates that the placebo effect highly unlikely to be driven by regression to the mean

A total of [redacted] patients who completed TONES 4 subsequently enrolled in the open label TONES 5 open label extension study after a break in treatment (as they stopped treatment upon completing TONES 4). The break in treatment between completing TONES 4 and enrolling in TONES 5 is unknown.

Figure 3 presents the mean ESS scores for these [redacted] patients throughout TONES 4 and subsequently throughout TONES 5.

- In TONES 4 (left panel), all patients received solriamfetol during the titration and stable dose phases (first four weeks) and had a significant reduction (i.e. improvement) in mean ESS scores.

- During the two-week randomised withdrawal phase (weeks 4 to 6) in TONES 4, patients randomised to placebo (blue line) experienced an increase (i.e. deterioration) in mean ESS, but patients randomised to continue solriamfetol (orange line) experienced no change in ESS score.
- At the end of the randomised withdrawal phase, mean ESS scores were placebo=[redacted] and solriamfetol=[redacted]. Upon completing TONES 4, these patients stopped receiving solriamfetol and after a break in treatment (duration unknown), subsequently enrolled into TONES 5 (right panel).
- A comparison of the mean ESS scores in TONES 4 vs TONES 5 shows that the baseline ESS scores for each trial fall within [redacted] point of each other:
  - For patients in TONES 4 who received placebo during the randomised withdrawal phase, baseline ESS in TONES 4 vs TONES 5 were [redacted] vs [redacted], respectively
  - For patients in TONES 4 who continued solriamfetol during the randomised withdrawal phase, baseline ESS in TONES 4 vs TONES 5 were [redacted] vs [redacted], respectively
- The similarity between baseline ESS scores indicates that neither baseline was a temporary extreme value (as would be expected if there were regression to the mean), but instead both reflect a true mean ESS for these patients.

In addition to indicating that the effect observed in the placebo arm of TONES 4 is not a regression to the mean, these data also demonstrate that patients who discontinue and subsequently restart solriamfetol can achieve repeat reductions (improvements) in ESS with rapid onset. As shown in Figure 3, after discontinuing solriamfetol treatment due to completing TONES 4, patients' ESS returned towards baseline. Within two weeks of restarting solriamfetol treatment in TONES 5, the patients experienced significant reductions (i.e. improvements) in mean ESS scores in TONES 5, with mean ESS scores reduced (improved) to levels similar to those previously achieved in TONES 4.

2.10.4.5. Additional evidence from TONES 4 demonstrating that the placebo effect is highly unlikely to be driven by regression to the mean

In TONES 4, patients randomised to continue solriamfetol treatment during the randomised withdrawal phase did not experience an increase in ESS score ([redacted] at week 4 vs [redacted] at week 6). Note that these patients did not exhibit a 'nocebo' effect – a psychological negative patient expectancy that their symptoms will worsen as a result of believing they were randomised to placebo (despite being randomised to active treatment) (36); treatment effect with solriamfetol is therefore robust to this neurobiological phenomenon.

Conversely, patients who were randomised to switch to placebo during the randomised withdrawal phase experienced a rapid increase in ESS scores upon switching to placebo and withdrawing from solriamfetol (from [redacted] at week 4 to [redacted] at week 6). The ESS scores for patients randomised to placebo (i.e. to withdraw from solriamfetol) returned toward an average ESS consistent with their baseline characteristic ESS. Subsequently, at the baseline of TONES 5, the mean ESS score for these patients was [redacted], demonstrating that with extended durations after solriamfetol withdrawal, patients eventually returned to a pre-treatment, true baseline ESS score.

The extensive clinical data presented above support a true placebo effect *and* a stable underlying disease state with consistent baseline ESS; unless the nadir of natural variation in reported symptom

severity happened to coincide perfectly with baseline ESS assessments in *both* TONES 4 and TONES 5. It is therefore highly unlikely that a regression to the mean contributed to the placebo effect.

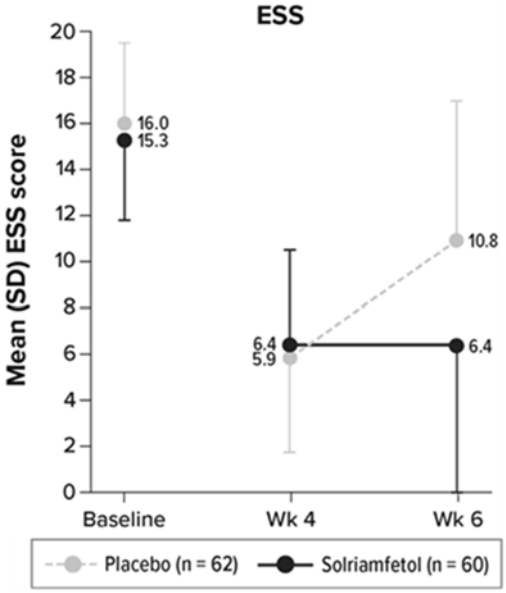
Figure 3. ESS scores over time for patients with OSA who completed TONES 4 and subsequently enrolled in TONES 5

Abbreviations: ESS, Epworth Sleepiness Scale; RW, randomised withdrawal phase.
a All patients were receiving solriamfetol from baseline to week 4 and then randomised 1:1 to solriamfetol or placebo (37). Baseline characteristics of the safety population in TONES 4 (ie, any participant who received ≥1 dose of solriamfetol in the titration phase) were consistent across the three phases of the study and were comparable between groups.
ESS score ranges from 0–24 where higher scores indicate higher levels of sleepiness, and ESS ≤ 10 are considered within the normal range.
The randomised withdrawal phase of TONES 5 is not shown however results were similar to TONES 4.

In ERG Response to TE, Issue 4, Section 2.4, the ERG stated that "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" and 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".

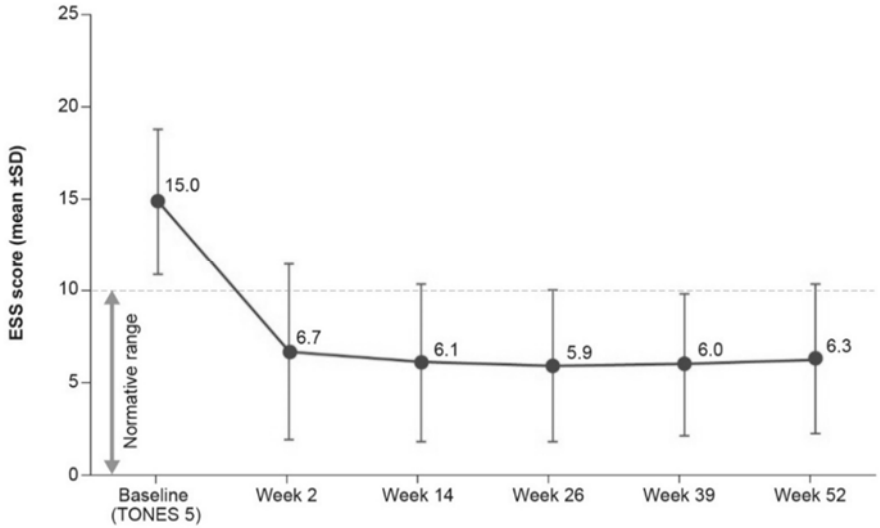
Although the population may have been open to selection bias, this was not a pre-specified analysis in the trial, however note that approximately [redacted]) of patients in TONES 4 subsequently enrolled in TONES 5, and these [redacted] patients formed the majority of the patients in TONES 5 Group B (Total patients in Group B =84; i.e. those patients who enrolled into TONES 5 following a break in treatment after completing a prior TONES study) (29). The ESS efficacy results for these [redacted] patients in TONES 4 (Figure 3) was broadly comparable to the TONES 4 overall results (Figure 4), and the efficacy for these patients in TONES 5 was broadly comparable to the TONES 5 overall results (Figure 5).

Figure 4. TONES 4: ESS at baseline and before/after 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 (37).

Figure 5. 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 2020 (29).

2.10.4.6. Evidence from patients who completed TONES 3 and TONES 4 who had both a screening and baseline ESS assessment for TONES 5

As mentioned above, TONES 5 was an open label extension study that enrolled patients who had previously completed another TONES study. A small group of patients who previously completed TONES 3 and TONES 4, and subsequently enrolled in TONES 5, had both a screening and a baseline ESS score for TONES 5 (Table 23; duration of time between assessments is unknown):

- For the 10 patients in TONES 3 with both measurements, mean ESS was [redacted] at screening and [redacted] at baseline
- For the 14 patients in TONES 4 with both measurements, mean ESS was [redacted] at screening and [redacted] at baseline

Table 23. Mean ESS scores at screening and baseline assessments in TONES 5, for patients who completed TONES 3 and TONES 4 and subsequently enrolled into TONES 5

	ESS score at screening assessment in TONES 5	ESS score at baseline assessment in TONES 5
TONES 3 (N=10)		
Mean (SD)	[redacted]	[redacted]
Median (Range)	[redacted]	[redacted]
TONES 4 (N=14)		
Mean (SD)	[redacted]	[redacted]
Median (Range)	[redacted]	[redacted]

Abbreviations: SD, standard deviation.
N numbers reflect the patients from each trial that had both a screening and baseline ESS score for TONES 5.
Duration of time between screening and baseline assessment of ESS is unknown.

The screening and baseline ESS scores for these patients fall within [redacted] point of each other (within each trial cohort), and are within ~1 point of the respective trial population means (TONES 3: placebo 15.6; solriamfetol 15.2; TONES 4: overall 15.4) (37). This demonstrates the relative stability of mean ESS scores over time (consistent with the evidence in Figure 3), and indicates that the mean ESS reductions observed in the placebo arms are unlikely to be regression to the mean.

Consistent with this, Jazz consulted a range of clinical experts on the natural variation in EDS as measured by ESS, and the clinicians informed us that in general it was expected that ESS would remain stable based on validated reproducibility in the clinical trial setting, that patients experience a sustained benefit from CPAP over time, and that any changes can be generally be attributed to non-OSA factors such as treatment or onset of depression, onset of periodic limb movement disorder (38).

2.10.4.7. The speed of placebo response is inconsistent with regression to the mean

The onset of the placebo effect observed in TONES 3 was rapid, occurring within the first week of the trial, and continuing to improve over subsequent time points. If regression to the mean were responsible for the improvements in ESS scores in the placebo arm, it is highly unlikely that this would occur in the first week as regression to the mean is expected to occur over a longer period of time.

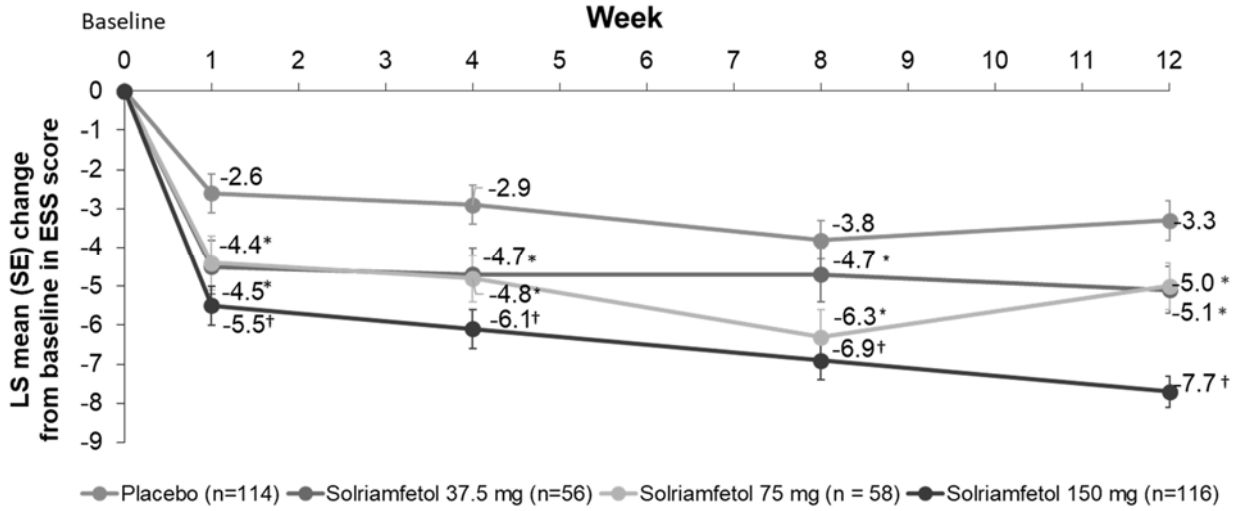
Furthermore, in considering the patient journey, the duration of time that would pass from a patient entering a temporary acute worsening of their ESS through to receiving placebo in the study suggests the placebo effect in the TONES trials are unlikely to reflect a regression to the mean:

1. A patient with diagnosed OSA notices that their residual EDS is having an acute, severe impact on their life
2. The patient makes a decision to enrol in a clinical trial for treatment for their residual EDS
3. Patient potentially consults their own primary or secondary care doctor treating their diagnosed underlying OSA
4. Patient is screened and enrolled in the trial
5. Patient receives placebo in the trial

Steps 1 to 5 above are likely to require an extended duration of time, thus it is unlikely the patients receiving placebo would subsequently experience a rapid reduction (i.e. improvement) in ESS within the first week of the trial (Figure 6), and continue to improve over the following 11 weeks.

This rapid onset of effect is also observed in TONES 4 (Figure 4) and combined with the evidence presented in Section 2.10.4.4 indicates that the baseline ESS scores in the trials are reflective of a true mean baseline and that regression to the mean is not contributing to the improvements in ESS observed in the placebo arm.

Figure 6: TONES 3: Change from baseline on the ESS at weeks 1, 4, 8, and 12 (mITT Population)



Abbreviations: LS, least squares; ESS, Epworth Sleepiness Scale; mITT, modified intent to treat; MMRM, mixed effects repeated measures; SE, standard error.
*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.

2.10.4.8. Conclusion

Following extensive examination of the TONES programme clinical data, the data show that there is little evidence to support the presence of a regression to the mean effect in the trials. Instead the data presented support a true placebo effect *and* a stable underlying disease state with consistent baseline ESS. Unless the nadir of natural variation in reported symptom severity happened to coincide perfectly with baseline ESS assessments in *both* TONES 4 and TONES 5, it is therefore highly unlikely that a regression to the mean contributed to the placebo effect. As such, the assumption of a Hawthorne effect in the Company's base case analysis (Table 1) can be considered a conservative approach that likely underestimates the true cost-effectiveness of solriamfetol.

P. Appendix P: Additional cost-effectiveness analyses: revised company base case, with solriamfetol revised PAS price post ACD stage

Appendix P supersedes Appendix O (Feb 2021). The results below reflect Jazz's revised base case at the time of the company's response to the ACD (June 2021) and include modifications to the assumptions in the original CS Form B, 17 Dec 2020.

A full list of the assumptions and a rationale for any modifications is provided in Table 2.

Appendix P, Table 1. 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)
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)

Variable	Value	Measurement of uncertainty and distribution: CI (distribution)
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]
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	[redacted]	[redacted]
Proportion of patients receiving solriamfetol 75 mg	[redacted]	[redacted]
Proportion of patients receiving solriamfetol 150 mg	[redacted]	[redacted]

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.

P.1 Base case results

Appendix P, Table 2. 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	£4,810	11.524	30.213			
Standard of care with the addition of solriamfetol ([redacted] 37.5, 75, 150 mg)	[redacted]	11.969	30.213	[redacted]	0.445	[redacted]

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

Appendix P, Table 3. 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	£4,792	11.480	30.033			
Standard of care with the addition of solriamfetol (37.5, 75, 150 mg)	[redacted]	11.923	30.033	[redacted]	0.443	[redacted]

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

P.2 Sensitivity analyses

P.2.1 Probabilistic sensitivity analysis

The probability that solriamfetol would be the most cost-effective treatment was 75% at a threshold of £20,000 per QALY, and was 99% at a threshold of £30,000 per QALY (Figure 24). Across 5,000 PSA simulations, solriamfetol was associated with a mean cost of £[redacted] (95% CI: [redacted]) and mean total QALYs of 12.398 (95% CI: 12.387, 12.408) (Appendix P, Table 4). These results are highly congruent with the deterministic results. Overall, the results remain consistent with the base case analysis.

Appendix P, Figure 1. Cost-effectiveness acceptability curve

Abbreviations: SoC, standard of care.

Appendix P, Table 4. Probabilistic sensitivity analysis results

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER incremental (£/QALY)
Standard of care without solriamfetol	£4,873 (£4,782 - £4,964)	11.866 (11.855 - 11.877)			
Standard of care with the addition of solriamfetol ([redacted] 37.5, 75, 150 mg)	[redacted]	12.398 (12.387 - 12.408)	[redacted]	0.531	[redacted]

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

P.2.2 Deterministic sensitivity analysis

Appendix P, Figure 2. 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

Appendix P, Table 5. 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 75 mg ([redacted]	[redacted]	[redacted]
Placebo - SAE ([redacted]% to [redacted]%; base case [redacted]%)	[redacted]	[redacted]
Proportion of patients on Sol 37.5 mg ([redacted])	[redacted]	[redacted]
Sol 37.5mg - SAE ([redacted]% to [redacted]%; base case [redacted]%)	[redacted]	[redacted]
NHWS mapping - ESS Score: 0-11 coeff ([redacted])	[redacted]	[redacted]
Sol 150mg - SAE ([redacted]% to [redacted]%; base case [redacted]%)	[redacted]	[redacted]
Discontinuation - LoE (Yr n): Sol 75 mg ([redacted])	[redacted]	[redacted]

Abbreviations: ESS, Epworth Sleepiness Scale; ICER, incremental cost effectiveness ratio; LoE, loss of efficacy.
Yr n refers to years 2 and beyond.

P.2.3 Threshold analysis

Appendix P, Table 6. Results of threshold analysis: standard of care with the addition of solriamfetol versus standard of care without solriamfetol

	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%)	1.9%	-1.3%*
NHWS mapping - ESS Score: 12-24 coeff	[redacted]	[redacted]	[redacted]
Discount rate: Outcomes	3.5% (0.0% to 6.0%)	5.4%	11.4%*
Proportion of patients on Sol 75 mg	[redacted]	[redacted]	[redacted]
Placebo - SAE	[redacted]	[redacted]	[redacted]
Proportion of patients on Sol 37.5 mg	[redacted]	-10.6%*	NA
Sol 37.5mg - SAE	[redacted]	[redacted]	[redacted]
NHWS mapping - ESS Score: 0-11 coeff	[redacted]	[redacted]	[redacted]
Sol 150mg - SAE	[redacted]	[redacted]	[redacted]
Discontinuation - LoE (Year n): Sol 75 mg	[redacted]	[redacted]	[redacted]

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.
Year n refers to years 2 and beyond.
* Outside credible range.
† As the other doses are varied independently these scenarios are implausible (as the total share will exceed 100%).

P.2.4 Scenario analyses

P.2.4.1 Alternative model time horizon

Appendix P, Table 7. Scenario analysis: Alternative model time horizon

Time horizon, years	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]

P.2.4.2 Alternative definition of response

Appendix P, Table 8. Scenario analysis: Response is a reduction in ESS ≥3 – Combined

Technologies	Total costs (£)	Total QALYs	LYG	Incremental costs (£)	Incremental QALYs	Incremental ICER
Standard of care without solriamfetol	£4,810	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.

Appendix P, Table 9. 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	£4,810	11.524	30.213			
Standard of care with the addition of solriamfetol	[redacted]	**11.874**	**30.213**	[redacted]	**0.351**	[redacted]

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

P.2.4.3 Disaggregated results utilising bootstrapping methods

Appendix P, Table 10. Results of the bootstrapping analysis on the raw mIPD – dose split [redacted]

Technology	Total costs (£)	Total QALYs	Total LYG	Incremental costs versus baseline (£)	Incremental QALYs versus baseline	ICER versus baseline (£/QALY)
Standard of care without solriamfetol	£4,792 (£4,788 - £4,796)	11.480 (11.470 - 11.490)	30.033 (29.992 - 30.074)			
Standard of care with solriamfetol 37.5 mg	[redacted]	11.756 (11.745 - 11.767)	30.033 (29.992 - 30.074)	[redacted]	0.276	[redacted]
Standard of care with solriamfetol 75 mg	[redacted]	11.866 (11.855 - 11.877)	30.033 (29.992 - 30.074)	[redacted]	0.110	[redacted]
Standard of care with solriamfetol 150 mg	[redacted]	12.205 (12.194 - 12.216)	30.033 (29.992 - 30.074)	[redacted]	0.339	[redacted]

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

P.2.4.4 Alternative solriamfetol dose splits

Appendix P, Table 11. 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	£4,810	11.524	30.213			
Standard of care with solriamfetol 37.5 mg	[redacted]	11.801	30.213	[redacted]	0.277	[redacted]
Standard of care with solriamfetol 75 mg	[redacted]	11.911	30.213	[redacted]	0.387	[redacted]
Standard of care with solriamfetol 150 mg	[redacted]	12.252	30.213	[redacted]	0.728	[redacted]

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

Appendix P, Table 12. Alternative solriamfetol dose split: 37.5 mg -40%, 75 mg-40%, 150 mg-20%

Technologies	Total costs (£)	Total QALYs	LYG	Incremental costs (£)	Incremental QALYs	Incremental ICER
Standard of care without solriamfetol	£4,810	11.524	30.213			
Standard of care with the addition of solriamfetol	[redacted]	**11.935**	**30.213**	[redacted]	**0.411**	[redacted]

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

Appendix P, Table 13. 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	£4,810	11.524	30.213			
Standard of care with the addition of solriamfetol	[redacted]	**11.988**	**30.213**	[redacted]	**0.464**	[redacted]

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

Appendix P, Table 14. Alternative solriamfetol dose split: 37.5 mg - 20%, 75 mg-40%, 150 mg-40%

Technologies	Total costs (£)	Total QALYs	Total LYG	Incremental costs (£)	Incremental QALYs	ICER versus baseline (£/QALY)
Standard of care without solriamfetol	£4,810	11.524	30.213			
Standard of care with the addition of solriamfetol (20/40/40 37.5, 75, 150 mg)	[redacted]	**12.025**	**30.213**	[redacted]	**0.501**	[redacted]

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

P.2.4.5 Alternative HRQoL estimates

OSA based QoL estimates from McDaid

Appendix P, Table 15. 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	£4,810	13.963	30.213			
Standard of care with the addition of solriamfetol	[redacted]	**14.346**	**30.213**	[redacted]	**0.383**	[redacted]

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

OSA based QoL estimates from time trade off analysis

Appendix P, Table 16. Scenario analysis: time trade off utilities - Combined

Technologies	Total costs (£)	Total QALYs	LYG	Incremental costs (£)	Incremental QALYs	Incremental ICER
Standard of care without solriamfetol	£4,810	12.028	30.213			
Standard of care with the addition of solriamfetol	[redacted]	**12.980**	**30.213**	[redacted]	**0.952**	[redacted]

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

P.2.5 Partner utilities

Appendix P, Table 17. 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	£4,810	20.605	30.213			
Standard of care with the addition of solriamfetol	[redacted]	**21.214**	**30.213**	[redacted]	**0.609**	[redacted]

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

Appendix P, Table 18. 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	£4,810	23.943	30.213			
Standard of care with the addition of solriamfetol	[redacted]	**24.467**	**30.213**	[redacted]	**0.524**	[redacted]

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

Appendix P, Table 19. Scenario analysis: time trade off patient utilities combined with partner utilities

Technologies	Total costs (£)	Total QALYs	LYG	Incremental costs (£)	Incremental QALYs	Incremental ICER
Standard of care without solriamfetol	£4,810	21.296	30.213			
Standard of care with the addition of solriamfetol	[redacted]	**22.599**	**30.213**	[redacted]	**1.303**	[redacted]

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

P.3 Subgroup analysis

P.3.1 Compliant or non-compliant to primary OSA therapy

Appendix P, Table 20. Scenario analysis: Compliant to a primary OSA therapy (at baseline of TONES 3) – solriamfetol combined

Technologies	Total costs (£)	Total QALYs	LYG	Incremental costs (£)	Incremental QALYs	Incremental ICER
Standard of care without solriamfetol	£4,720	11.382	29.301			
Standard of care with the addition of solriamfetol	[redacted]	**11.775**	**29.301**	[redacted]	**0.393**	[redacted]

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

Appendix P, Table 21. Scenario analysis: Non-compliant to a primary OSA therapy (at baseline of TONES 3) – solriamfetol combined

Technologies	Total costs (£)	Total QALYs	LYG	Incremental costs (£)	Incremental QALYs	Incremental ICER
Standard of care without solriamfetol	£4,982	11.767	32.026			
Standard of care with the addition of solriamfetol	[redacted]	**12.318**	**32.026**	[redacted]	**0.550**	[redacted]

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

Consultation on the appraisal consultation document – email: **NICE DOCS**

Checklist for submitting comments

Use this comment form and submit it as a Word document (not a PDF).

Complete the disclosure about links with, or funding from, the tobacco industry.

Combine all comments from your organisation into 1 response. We cannot accept more than 1 set of comments from each organisation.

Do not paste other tables into this table – type directly into the table.

Please underline all confidential information, and separately highlight information that is submitted under [redacted] and all information submitted under [redacted]. If confidential information is submitted, please also send a 2nd version of your comment with that information replaced with the following text: 'academic / commercial in confidence information removed'. See the Guide to the processes of technology appraisal (section 3.1.23 to 3.1.29) for more information.

Do not include medical information about yourself or another person from which you or the person could be identified.

Do not use abbreviations

Do not include attachments such as research articles, letters or leaflets. For copyright reasons, we will have to return comments forms that have attachments without reading them. You can resubmit your comments form without attachments, it must send it by the deadline.

If you have received agreement from NICE to submit additional evidence with your comments on the appraisal consultation document, please submit these separately.

Note: We reserve the right to summarise and edit comments received during consultations, 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 our consultations 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.

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ID1499: Company response to additional ERG queries made on Thursday 5 August 2021 11:38

Question 1 received from NICE:

Regarding the model that has been submitted , 'ID1499_Solriamfetol Hawthorne_with SAE 280621', the ERG can only produce results for the base case assuming 100% 'Hawthorne' and the scenario with 100% 'pure placebo. The model doesn't show how you have coded the regression to the mean scenario or how you have calculated the combinations of the three mechanisms in table 6 of the ACD response. Are you able to provide a model that was used to produce the results in table 6 of the ACD response and instructions on how to conduct this analysis please?

Response to Question 1

The zip folder provided ("ID1499_AdditionalModels_6Aug2021") contains four files:

1. ID1499_Solriamfetol_Hawthorne_with_SAE_280621.xlsm
2. ID1499_Solriamfetol_TruePlacebo_with_SAE_280621.xlsm
3. ID1499_Solriamfetol_RTM_with_SAE_280621.xlsm
4. Combination_Workbook_Live_280621.xlsx

Ideally the zipped file should be extracted to the C drive of the machine in use – This should maintain the linkage between the files.

If the links between the workbooks and the **Combination_Workbook_Live_280621** become broken then the tabs in the **Combination_Workbook_Live_280621** will need to be relinked to the appropriate scenario file:

e.g. For the **Hawthorne_Results** tab the cells **D10:F13** need to be linked to the corresponding cell range in the **Results** tab of **ID1499_Solriamfetol_Hawthorne_with_SAE_280621.xlsm**)

The file **ID1499_Solriamfetol_20210528_Hawthorne** is the same file provided previously (with the ACD response) and the file **ID1499_Solriamfetol_TruePlacebo_with_SAE_280621** is the same as this but utilising the unadjusted data for solriamfetol.

The file **ID1499_Solriamfetol_RTM_with_SAE_**280621 has been modified as detailed in the ACD response.

Finally, the file **Combination_Workbook_Live_280621** is a linked workbook with a separate sheet pulling in the respective results from each corresponding models **Results** tab.

In this file the tab **Combined_Results** weights the results from the 3 scenarios (Hawthorne, True placebo and RTM) to provided the scenario results provided in the ACD (please note this uses the Excel Data Table functionality and so the user may need to press F9 to update these calculations depending on local machine settings)

There are separate tabs where the results for each of the market share scenarios have been recorded.

Please note: To generate these results the settings of each of the scenario workbooks (1-3 above) need to align (e.g. the price, market share, and any other settings).

There are checks on the **Combined_Results** tab for Price (E10:E11) and Market share (G9:G11) as these were the key parameters being changed however, other scenarios can be considered through appropriate amendments to **all** 3 scenario models.

Question 2 received from NICE:

Are you also able to explain how you obtained the subgroup results in tables 4 and 5 of the ACD response please? And why they are different from those reported in tables 20 and 21 please?

Response to Question 2

The Committee asked the Company to provide the clinical and cost-effectiveness of **solriamfetol alone for people who cannot tolerate CPAP**. The Company believes this would include the subgroup of patients described by the clinical expert in ACD 3.17 (people with mental health or neurodegenerative conditions who may be unable to adequately use CPAP regularly).

This was not a prespecified analysis in the TONES 3 trial, and the trial data did not lend itself to directly assessing this issue. However, in order to meet this request, the Company used TONES 3 data as a proxy for patients who (in practice) may not be using a primary OSA therapy. To conduct the analysis, the IPD for TONES 3 was categorised into two subgroups:

(i) patients who were using a primary OSA therapy at baseline
(ii) patients who were not using a primary OSA therapy at baseline

Note that this analysis **does not** categorise patients according to their *level of use* (i.e. compliance) of their primary OSA therapy. Tables 4 and 5 of the Company response to ACD, respectively, present the results of this analysis.

In contrast to the analysis described above, Appendix P, Tables 20 and 21 reflect a different analysis based on a different subgroups of patients. This analysis **does** categorise patients according to their *level of use* (compliance) of a primary OSA therapy. Compliance was defined as device use for ≥ 4 hours per night on ≥ 70% of nights (for devices with downloadable data), or device use on ≥ 70% of nights (for devices with no downloadable data), or effective surgical intervention".

Although there is some overlap in the populations assessed in each of the two analyses, the subgroups of patients and therefore the cost-effectiveness results are different. For clarity a table describing the distinction is shown below.

Analysis 1: Using vs Not Using a primary OSA therapy at baseline (ACD Response Tables 4–5)	**Analysis 2: Compliant vs noncompliant to a primary OSA therapy at baseline (ACD Response Appendix P, Tables 20–21)**
A person using a CPAP machine at baseline is "using" a primary OSA therapy*, regardless of their level of use of that therapy*	A person using a CPAP machine at baseline is "using" a primary OSA therapy and *subsequently further categorised* into "compliant" or "non-compliant"

Model instructions for these analyses

The results reported in Appendix P, Table 20 and 21 can be generated using the dropdown on the **Results** tab of the **ID1499_Solriamfetol_Hawthorne_with_SAE_280621.xlsm** (Option: Compliant/Non-complaint, respectively).

The new results presented in Table 4 and 5 were generated utilising this same functionality but replacing the OSA compliant records (column M of the **_IPD_OSA** tab) with the OSA therapy at baseline fields. To replicate the functionality, the fields in column M were replaced with a formula (*Cell M6: =IF(Y6="Y","Compliant","Non-compliant"*) and replicated for all records. A separate version of the model in a state to generate the results shown in ACD response Table 4 and 5 has been provided: **ID1499_Solriamfetol_Hawthorne_with_SAE_280621_ALT**

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

Consultation on the appraisal consultation document – deadline for comments 5pm on Wednesday 28 April **email:** NICE DOCS

	Please read the checklist for submitting comments at the end of this form. We cannot accept forms that are not filled in correctly. The Appraisal Committee is interested in receiving comments on the following: • has all of the relevant evidence been taken into account? • are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence? • are the provisional recommendations sound and a suitable basis for guidance to the NHS? NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that the preliminary recommendations may need changing in order to meet these aims. In particular, please tell us if the preliminary recommendations: • could have a different impact on people protected by the equality legislation than on the wider population, for example by making it more difficult in practice for a specific group to access the technology; • could have any adverse impact on people with a particular disability or disabilities. Please provide any relevant information or data you have regarding such impacts and how they could be avoided or reduced**.**
Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	**British Thoracic Society**
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	None
Name of commentator person completing form:	[redacted]

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

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	Insert each comment in a new row. Do not paste other tables into this table, because your comments could get lost – type directly into this table.
Example 1	We are concerned that this recommendation may imply that ……..
1	We note that the following reference has not been included: Effects of Solriamfetol on Quality-of-Life Measures from a 12-Week Phase 3 Randomized Controlled Trial Terri E. Weaver et al Annals ATS Volume 17 Number 8 August 2020
2	The provisional recommendations are appropriate.
3	
4	
5	
6	

Insert extra rows as needed

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- Complete the disclosure about links with, or funding from, the tobacco industry.
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- Do not paste other tables into this table – type directly into the table.
- Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise and all information submitted under 'academic in confidence' in yellow. If confidential information is submitted, please also send a 2nd version of your comment with that information replaced with the following text: 'academic / commercial in confidence information removed'. See the Guide to the processes of technology appraisal (section 3.1.23 to 3.1.29) for more information.
- Do not include medical information about yourself or another person from which you or the person could be identified.
- Do not use abbreviations
- Do not include attachments such as research articles, letters or leaflets. For copyright reasons, we will have to return comments forms that have attachments without reading them. You can resubmit your comments form without attachments, it must send it by the deadline.
- If you have received agreement from NICE to submit additional evidence with your comments on the appraisal consultation document, please submit these separately.

Note: We reserve the right to summarise and edit comments received during consultations, 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 our consultations 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.

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NICE National Institute for Health and Care Excellence

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

Consultation on the appraisal consultation document – deadline for comments 5pm on Wednesday 28 April **email:** NICE DOCS

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Comments on the ACD received from the public through the NICE Website

Name	[redacted]
Comments on the ACD:	

Has all of the relevant evidence been taken into account?
I am disappointed to hear that the provisional decision is that solriamfetol will not be made available on the NHS. I am a sleep apnoea sufferer myself who, despite high usage of CPAP, finds myself continuing to experience fatigue, and was informed by my consultant that this drug may be available going forward. One thing that does seem to have been overlooked is the fact that currently other than CPAP there is nothing that the NHS can offer patients if CPAP fails to remedy their issues. Modafinil used to be available on the NHS but this was withdrawn long before I (and others) were diagnosed, meaning it's not readily available to patients like me. Additionally, modafinil can't always be tolerated by people. I paid out of my own pocket to be able to try the drug and it worked for a period of time, but it eventually stopped working, so to have solriamfetol available for people to try would give patients options. Whilst I understand NICE's concerns around the cost of the drug, you need to bear in mind that if the cost is prohibitive for the NHS then it certainly would be for patients also - the NHS, through economies of scale, would be able to secure the drugs cheaper than a patient would and it's not going to be affordable to patients otherwise. Rather than preventing the people who need it from accessing the drug, a far better system would be to only offer it to those who can demonstrate they still have issues even when they have high usage of CPAP. I know that I have already gotten my CPAP usage as high as it can go, as I'm using it most nights but sometimes I can fall asleep without it as I'm too tired to put my mask on or I take it off mid-sleep without being awake enough to realize. Remember also that whilst there may be an upfront cost for this drug to the NHS, sleep apnoea is linked to many adverse impacts for individuals - for example, many patients struggle to exercise regularly due to fatigue which can lead to all manner of health issues - so the NHS would see a cost for having to treat those patients. I personally have noticed that my lifestyle has been less active since my diagnosis. The fatigue can be crippling - I often have to have mid day naps just to get through day but often these sleeps are unrefreshing leaving me feeling no better even after the nap. It's not an understatement to say that I have not been able to have a normal life since my diagnosis. Whilst there is often an assumption that this is an illness that only affects the old or overweight, I was diagnosed in my mid-twenties at a normal BMI, so there are young people who's life is being ruined by this condition. The fact that I need the CPAP equipment anytime I sleep acts as an extra barrier to having a normal life as it is something I need with me always. If I have to go somewhere and can't take my CPAP with me then my condition would deteriorate worse than it already is, each day that I didn't use the machine. To have a drug that I could take when CPAP is not an option would improve my quality of life. Whilst people often think sleep apnoea is something minor that can be remedied, the truth is that it's a serious condition whereby you can stop breathing in your sleep, leaving you

drained the next day with headaches and other symptoms and yet there are no drugs available at the moment on the NHS for it. I believe making solriamfetol available would help improve the quality of life of many sleep apnoea sufferers. I hope the decision will be reconsidered.

Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?
See above.

Are the recommendations sound and a suitable basis for guidance to the NHS?
See above.

Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity?
Disability discrimination - there are many people who cannot work or live normal lives due to sleep apnoea and co-morbidities so without offering any care, beside CPAP, that leaves people without any options.

CONFIDENTIAL UNTIL PUBLISHED

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

Solriamfetol for treating excessive waketime sleepiness caused by obstructive sleep apnoea

Evidence Review Group's critique of the company's response to the appraisal consultation document (August 2021)

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Date completed	30 August 2021

Commercial in confidence (CIC) information in blue

Academic in confidence (AIC) information in yellow

1. Introduction

This document is the ERG critique of the response by the company, Jazz Pharmaceuticals, to the NICE appraisal consultation document (ACD) (Issue date: April 2021) for the technology appraisal on solriamfetol for treating excessive waketime sleepiness caused by obstructive sleep apnoea [ID1499]. The ERG received the company's ACD response form and revised model on 28th June 2021. In response to ERG questions, the company provided further information and additional versions of the economic model on 9th August 2021.

2. ERG validation of cost-effectiveness results

2.1. Revised base case analysis

The company has proposed a revised cost-effectiveness base case which gives an ICER of [redacted] per QALY gained for solriamfetol with standard care versus standard care alone (Table 1 ACD response). This compares with the company's previous base case ICER of [redacted] per QALY, which they had revised in their response to technical engagement.

Changes to the previous company base case are described in Table 2 of their ACD response:

- A revised PAS discount for solriamfetol
- Definition of treatment response: ESS reduction ≥ 2 (previously ≥ 3)
- Introduction of hospital costs associated with serious adverse events (SAEs), which the company based on TONES 3 safety data (rather than TONES 5 as in the ERG's preferred analysis).
- Increased proportions of patients assumed to be on higher doses of solriamfetol: [redacted] on 75 mg and [redacted] on 25 mg (previously 40% and 20% respectively)

Other changes to the base case listed in Table 2 of the ACD response had already been implemented in the company's response to technical engagement:

- Population with baseline ESS>12
- Dose specific loss of efficacy estimated from TONES 5
- Dose specific discontinuation rates estimated from TONES 5

The revised base case reflects the committee's preferred assumptions as listed in section 3.16 of the ACD (although the included SAE hospital costs differ from the ERG's estimates that were considered by the committee).

We show the cumulative effect of the company's changes to the base case in Table 1 below. These results were produced by the ERG, working backwards from the company's revised base case submitted with their ACD response (model dated 28/06/21). There is a small discrepancy for the ICER for the previous base case compared with that reported in the company's response to technical engagement ([redacted] versus [redacted]). This is caused by rounding of solriamfetol discontinuation rates in the new version of the model, which is not a matter of concern.

The revised PAS has the largest impact, reducing the ICER to below the £20,000 per QALY threshold. The increase in the assumed proportions of patients taking the higher doses of solriamfetol causes a moderate increase in the ICER. The introduction of costs for SAE hospitalisations causes a moderate fall in the ICER because the company estimated this cost from SAE-related admissions in the 12-week TONES 3 trial, which were higher in the placebo arm than in the solriamfetol arms (see Comment 6 in the company's ACD response, and ERG discussion in section 3.6 below). The broader definition of response (ESS reduction ≥ 2) causes a small increase in the ICER.

Table 1 Cumulative changes to base case: deterministic with PAS for solriamfetol

Cumulative changes to assumptions	Treatment	Total		Incremental		£ per QALY gained	
		Costs	QALYs	Costs	QALYs	ICER	Change
Previous base case [a]	SC alone	£0	11.524				
	SC + Sol	[redacted]	11.906	[redacted]	0.382	[redacted]	
+ Response (ESS reduction ≥2)	SC alone	£0	11.524				
	SC + Sol	[redacted]	11.935	[redacted]	0.411	[redacted]	[redacted]
+ Dose split (50% on 75 mg)	SC alone	£0	11.524				
	SC + Sol	[redacted]	11.969	[redacted]	0.445	[redacted]	[redacted]
+ SAE hospital costs (TONES 3)	SC alone	[redacted]	11.524				
	SC + Sol	[redacted]	11.969	[redacted]	0.445	[redacted]	[redacted]
+ Revised PAS, (new base case)	SC alone	[redacted]	11.524				
	SC + Sol	[redacted]	11.969	[redacted]	0.445	[redacted]	[redacted]

Source: produced by the ERG from the model submitted with company's ACD response (dated 28/06/21)

[a] The small difference in results compared to the post-technical engagement version of the company's model (dated 23/02/21) is due to rounding of solriamfetol discontinuation rates in the new model version

Abbreviations: SC standard care; Sol solriamfetol; SAE serious adverse events; PAS patient access scheme.

2.2. Sensitivity analysis

The company report a probabilistic ICER of [redacted] per QALY for their revised base case (ACD response Appendix Table 4). This is slightly higher than the deterministic estimate. The estimated probability that the base case ICER is below the committee's preferred threshold of £20,000 per QALY is 75%. The ERG found similar results on re-running the probabilistic sensitivity analysis.

Deterministic sensitivity analysis (Appendix Figure 2 and Table 5) indicates that results are most sensitive to uncertainty over the following parameters (with ICERs above the £20,000 per QALY threshold at either the upper or lower parameter limit):

[redacted]

2.3. Scenario and subgroup analyses

The committee highlighted key sources of uncertainty and requested additional analysis in sections 3.15 and 3.19 of the ACD. The company presented a number of subgroup and scenario analyses to address these uncertainties, which we summarise in Table 2 below.

Table 2 Subgroup and scenario analyses: deterministic with PAS for solriamfetol

		Total		Incremental		ICER	*ACD response source*
Scenario	**Treatment**	**Costs**	**QALYs**	**Costs**	**QALYs**	**£ / QALY**	
Revised base case	SC alone	£4,810	11.524				*Table 1*
	SC + Sol	[redacted]	11.969	[redacted]	0.445	[redacted]	
Subgroup analysis by use of primary OSA therapy at baseline							
Used	SC alone	£4,811	11.575				*Table 4*
	SC + Sol	[redacted]	11.991	[redacted]	0.415	[redacted]	
Not used	SC alone	£4,810	11.373				*Table 5*
	SC + Sol	[redacted]	11.893	[redacted]	0.521	[redacted]	
Subgroup analysis by compliance with primary OSA therapy at baseline							
Compliant	SC alone	£4,720	11.382				*Appendix Table 20*
	SC + Sol	[redacted]	11.775	[redacted]	0.393	[redacted]	
Not compliant	SC alone	£4,982	11.767				*Appendix Table 21*
	SC + Sol	[redacted]	12.318	[redacted]	0.550	[redacted]	

Scenario	Treatment	Total		Incremental		ICER	*ACD response source*
		Costs	QALYs	Costs	QALYs	£ / QALY	
Alternative placebo mechanisms							
True placebo	SC alone	£4,810	11.524				*Table 6*
	SC + Sol	[redacted]	12.222	[redacted]	0.699	[redacted]	
Regression to the mean	SC alone	£4,810	12.400				*ERG*
	SC + Sol	[redacted]	12.690	[redacted]	0.290	[redacted]	
Equal mixture of 3 mechanisms	SC alone	£4,810	11.816				*ERG*
	SC + Sol	[redacted]	12.294	[redacted]	0.478	[redacted]	
Solriamfetol dose split (37.5 mg / 75 mg / 150 mg)							
40/40/20	SC alone	£4,810	11.524				*Table 9*
	SC + Sol	[redacted]	11.935	[redacted]	0.411	[redacted]	
33/33/33	SC alone	£4,810	11.524				*Table 11*
	SC + Sol	[redacted]	11.988	[redacted]	0.464	[redacted]	
20/40/40	SC alone	£4,810	11.524				*Table 13*
	SC + Sol	[redacted]	12.025	[redacted]	0.501	[redacted]	
Hospitalisation costs for SAEs (annual % admitted, weighted by dose split for sol)							
SC 0% Sol [redacted]	SC alone	£0	11.524				*Table 16*
	SC + Sol	[redacted]	11.969	[redacted]	0.445	[redacted]	
SC 13.63% Sol [redacted]	SC alone	£8,884	11.524				*Table 17*
	SC + Sol	[redacted]	11.969	[redacted]	0.445	[redacted]	
SC 0% Sol [redacted]	SC alone	£0	11.524				*Table 18*
	SC + Sol	[redacted]	11.969	[redacted]	0.445	[redacted]	
Source of utility estimates							
McDaid ESS to EQ-5D mapping	SC alone	£4,810	13.963				*Appendix Table 15*
	SC + Sol	[redacted]	14.346	[redacted]	0.383	[redacted]	
Time trade off	SC alone	£4,810	12.028				*Appendix Table 16*
	SC + Sol	[redacted]	12.980	[redacted]	0.952	[redacted]	
Addition of partner utilities							
NHWS ESS to EQ-5D mapping	SC alone	£4,810	20.605				*Appendix Table 17*
	SC + Sol	[redacted]	21.214	[redacted]	0.609	[redacted]	
McDaid ESS to EQ-5D mapping	SC alone	£4,810	23.943				*Appendix Table 18*
	SC + Sol	[redacted]	24.467	[redacted]	0.524	[redacted]	
Time trade off	SC alone	£4,810	21.296				*Appendix Table 19*
	SC + Sol	[redacted]	22.599	[redacted]	1.303	[redacted]	

Source: Company's ACD response, checked by the ERG using submitted models dated 09/08/21

Abbreviations: SC standard care; Sol solriamfetol; PAS patient access scheme.

The ERG successfully replicated all of these results using versions of the model submitted by the company with their ACD response. We discuss and critique these analyses in the following sections of this report.

We note that the company did not provide further cost-effectiveness analysis in relation to the following committee requests:

- The effect of solriamfetol on adherence to primary OSA therapy (ACD 3.6)
- Use of SF-6D data from the company's trials to assess quality of life (ACD 3.11)
- Impact of partner utilities using EQ-5D (ACD 3.12)

3. ERG critique of company ACD comments

3.1. Comment 1: Evidence for solriamfetol alone for people who cannot tolerate CPAP

The committee asked the company to provide clinical and cost-effectiveness evidence for solriamfetol alone for people who cannot tolerate continuous positive airway pressure (CPAP) devices, as the marketing authorisation for solriamfetol includes people who may not be using a primary OSA therapy (ACD 3.7).

3.1.1 Subgroup analysis according to use of primary OSA therapy at baseline

In response to this request, the company provided cost-effectiveness estimates for subgroups from the TONES 3 trial who were using primary OSA therapy at baseline and those who were not (ACD response section 2.1). They argue that this provides a proxy for comparison of results for patients who can/ cannot tolerate CPAP.

The definition of primary OSA therapy in this analysis is not explicit, although the company notes that of the patients classified as using primary OSA therapy at baseline, 92% were using PAP, 2% "non-PAP" and 6% "device not specified". They also note that diet and lifestyle modifications were not recorded in TONES 3.

The proportions of responders and non-responders to solriamfetol and the mean change in ESS from baseline in the primary OSA use subgroups are shown in ACD response Table 3. This uses 'centred' individual patient data (IPD) for ESS at 12 weeks in accordance with the base case assumption that the placebo response was caused by observation bias ('Hawthorne' effect). Hence for the placebo arm, by definition there are no 'responders' and the mean change in ESS from baseline is recorded as zero in both subgroups.

We extracted further information on the subgroups classified as using/ not using primary OSA therapy at baseline using IPD from the model (Table 3 below). This dataset comprised [redacted] of patients in the TONES 3 modified ITT population. Of these patients, [redacted] were reported as not using primary OSA therapy at baseline. As might be expected, mean baseline ESS was higher for people who were not using primary OSA therapy at baseline than for people who were.

Table 3 TONES 3 subgroups using/not using primary OSA therapy at baseline

Study arm	N	Using primary OSA therapy				Not using primary OSA therapy			
		n	Age	Female	ESS	n	Age	Female	ESS
Placebo	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Sol (37.5 mg)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Sol (75 mg)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Sol (150 mg)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
All solriamfetol	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Source: extracted from company model (ALT version dated 09/08/21) by ERG

The results in ACD response Tables 3, 4 and 5 suggest that for people not using primary OSA therapy at baseline, solriamfetol was more cost-effective than for patients who were: ICER of [redacted] versus [redacted]

3.1.2 Subgroup analysis by adherence to primary OSA therapy at baseline

As in their original submission, the company report subgroup analysis for TONES 3 patients classified as compliant/ non-compliant with primary OSA therapy at baseline (Appendix P Tables 20 and 21 of the ACD response). This analysis is based on the same IPD dataset of [redacted] patients from the model as in Table 3 above, of whom [redacted] were classified as non-compliant with primary OSA therapy at baseline. The results suggest that solriamfetol was more cost-effective for patients who were not compliant with primary OSA therapy at baseline than for patients who were: ICER [redacted] versus [redacted]. There is some confusion over the precise definition of baseline primary OSA therapy compliance for this analysis, as the company cite definitions with some differences in sections 2.2.1 and 2.2.2 of their ACD response and reply to ERG questions dated 09/08/21.

ERG conclusion: The company argues that their analysis of TONES 3 trial data for subgroups who were/ were not using primary OSA therapy at baseline shows that solriamfetol is cost-effective for both groups. This is true, although this analysis was based on a small number of people not taking primary OSA therapy at baseline. We also note that

the analysis cannot distinguish according to the reason for non-use of primary OSA therapy at baseline (e.g., CPAP intolerance, neurodegenerative or mental health conditions).

3.2. Comment 2: The effect of solriamfetol on adherence to primary therapy

The NICE appraisal committee concluded that compliance to a primary OSA therapy like CPAP is unlikely to be affected by treatment with solriamfetol, but that more data were needed, including sensitivity analyses to assess the impact of missing data (ACD 3.6).

3.2.1 Company sensitivity analyses to explore the impact of missing data on adherence to primary OSA therapy

In response to the ACD, the company provide an additional sensitivity analysis to address the impact of the "small amount of missing data" using a conservative 'worst-case' approach.

- Missingness of data was assumed "not at random", but dependent on random allocation to treatment or control arms. Data were imputed as non-compliant for missing patients in the solriamfetol arm and compliant for the placebo arm.
- Participants compliant to primary OSA therapy at baseline and who received solriamfetol demonstrated [redacted] hours per night by week 12.
- The company benchmark this reduction against the general definition of compliance with PAP as being use on ≥4 hours on 70% of nights. Despite this being a 'worst case' scenario, they conclude that compliance "remains reassuringly exceeded".

The ERG assumes this analysis has been conducted using data from the parent study (TONES 3) rather than the population used in the analysis in the Schweitzer 2020 manuscript (TONES 5).[1 2] Thus, the results are based on the solriamfetol arm only (no corresponding value is given for the placebo arm). In the ERG's opinion the company's sensitivity analysis has a number of potential limitations:

- The analysis is restricted to those who were compliant with primary OSA therapy at baseline, and not those who were not fully compliant.
- Limited details are given for the type of imputation model used. In particular, it is not explicit how the binary distinction of 'compliant/non-compliant' translates into changes in a continuous measure (i.e., hours of sleep per night).
- The imputation increased the number of patients in the analysis considerably from [redacted] suggesting that the amount of missing data was not "small".
- No measure of variability or precision is given for the estimated compliance values.

- The company report results only for the 'number of hours per night of use' measure of compliance and not the other two measures (percentage of nights; percentage of nights with use ≥50%/night).
- Results are reported up to 12 weeks of solriamfetol treatment. There was no analysis of longer-term compliance (e.g., up to week 52 of treatment)

3.2.2 Query over missing data in the Schweitzer 2021 manuscript

At technical engagement, the company provided a journal manuscript (Schweitzer et al. Journal of Clinical Sleep Medicine 2020)[1] reporting analyses from the TONES 5 open label study. They cite this paper as supporting evidence to demonstrate that use of solriamfetol has no material effect on compliance with primary OSA therapy. The ERG's appraisal of the manuscript concluded that the potential impact of solriamfetol on use of primary OSA device therapy remained unclear because of uncertainty over factors such as the number of trial participants eligible for analysis; whether results differ for patients who were non-adherent to their device at baseline and potential bias due to missing data.

The company's response to the ACD has only partly resolved these uncertainties. Firstly, it remains unclear from Schweitzer et al. 2021 which patients were included in the analysis of primary OSA therapy use. The analysis of trial efficacy outcomes (ESS, CGI-c, PGI-c) are clearly stratified by the trial definition of adherence (n=251) and non-adherence (n=78) in the manuscript. It is less clear to the ERG from the manuscript which base population was used in the analysis of use of primary OSA therapy i.e. the results in Table 2.

The manuscript states "For participants using devices as primary OSA therapy (at any level of adherence), usage during the study was obtained by digitally recorded output from a positive airway pressure (PAP), oral appliance, or hypoglossal nerve stimulator device, when available, or by diary." The ERG assume that this analysis focused on device use and therefore excluded patients with surgical intervention. However, it appears that patients were included regardless of adherence to their device. The number of patients this applies to (and thus the denominator for this analysis) is not clearly described. As previously suggested, the ERG would have preferred to see this analysis also stratified by adherence (to device use) at baseline if possible.

[1] NB. In their response to the ACD, the company cites this manuscript as Schweitzer et al. 2021 (in the journal Chest). The ERG believes this to be a citation error as the publication in Chest reports data for the TONES 3 trial, rather than the open-label TONES 5 trial. Instead, the ERG assumes that the company intended to cite the Schweitzer et al. Journal of Clinical Sleep Medicine Published Online version :February 1, 2021, which supersedes the pre-publication accepted version from 2020.

Secondly, the manuscript states “Missing data were imputed using a last observation-carried-forward approach for the ESS, PGI-C, and CGI-C, but not for the FOSQ-10. Primary OSA therapy device use was summarized descriptively.” It remains somewhat unclear from the manuscript whether a last observation-carried-forward approach was actually applied in the analysis in the event of a missing data point for primary OSA therapy device usage.

The ERG understands that not all patients would have had electronically retrievable data and that data for some patients would only have been available by diary entry. Thus, the denominator varies according to the different measures of recording device use. However, according to Table 2 of the manuscript there still appears to be substantial missing data regardless of how device use was recorded:

- For the **% of nights of device use** measure, data were captured using either electronic or diary data. At baseline, 235 patients provided data but at the last time period only 186 patients had non-missing data and the change from baseline at this time point appears to include only 171 patients (62+109). Thus, it appears that **27%** of patients had missing data for the change from baseline to the last data point.
- For the **number of hours per night** measure of device use, data were only captured electronically and so the analysis was conducted in a smaller population. Of the 147 patients with electronic data at baseline, only 92 (34+58) had non-missing data for the change from baseline at the last time point (i.e. **37%** had missing data).
- For the **% of nights with device used for more than half the night** measure, data were captured only by diary. The % of patients with missing data for this measure for the change from baseline at the last data point was **28%**

Regardless of the means of data capture, at least a quarter of patients appeared to have missing data for the change from baseline analyses at the last time period. As per the ERG response at technical engagement, we note that 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”. This is somewhat ambiguous and may infer that there was no imputation for diary data.

ERG conclusion: The company’s ‘worst-case’ scenario to explore the impact of missing data on adherence to primary OSA therapy indicates that adherence remained at acceptable levels. However, the ERG regards the results as uncertain due to a number of limitations in the reporting of this analysis. The company’s response to the ACD has only partly addressed

the uncertainties raised by the ERG about missing data in the Schweitzer et al. 2021 manuscript.

3.3. Comment 3: Assessment of the potential impact of regression to the mean

In TONES 3, there was an improvement in ESS score from baseline to week 12 in the placebo arm, as well as in the solriamfetol treatment arms. The Company stated that although they believe that the placebo arm response was caused by a 'true' placebo effect, they adopted the more conservative assumption of an observation (or Hawthorne) effect for their base case.

The Hawthorne model uses a 'centring' approach to adjust both placebo and solriamfetol results from the trial:

- assuming no change in ESS from baseline to 12 weeks for patients treated with standard care alone; and
- reducing the improvement in ESS for patients treated with solriamfetol by subtracting the observed placebo arm improvement.

The company also reported a scenario with a 'true placebo' version of the model in their original submission. This is more favourable for solriamfetol than the base case because it includes the assumption of no ESS improvement for patients treated with standard care but makes no adjustment to the observed trial results for the solriamfetol arms.

In the ERG report, we questioned whether centring was 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' (RTM) effect. In the ERG preferred analysis, we adopted this more conservative RTM approach by using the raw unadjusted trial data: assuming that the response to treatment in TONES 3 would be the same in routine practice. To implement this approach, we developed a 4-state model, which allowed for changes in ESS over time for both intervention and comparator arms.

3.1.3 Company sensitivity analysis of alternative placebo mechanisms

In response to a request from the NICE committee, the company has now developed an alternative RTM version of their model and conducted sensitivity analyses, varying the relative contribution of each of the three potential placebo mechanisms (true placebo, Hawthorne and RTM) – ACD response Table 6. The ERG replicated the results in this table using the submitted versions of the three models and combination workbook (dated

09/08/21). The company presents results over a limited range of contribution from the regression to the mean mechanism (0% to 33%). We note that if this contribution is increased to 40% or higher, the ICER is greater than the £20,000 per QALY threshold, regardless of the residual contributions from the true placebo and Hawthorne mechanisms.

3.1.4 ERG critique of the company's regression to the mean model

The company's RTM model uses the following assumptions:

- Under standard care, there is a mean reduction from baseline to 12 weeks of [redacted] points (as in the placebo arm of the trial). This ESS improvement is assumed to persist for the lifetime of the model.
- In the solriamfetol arms, patients are classified as responders or non-responders. For patients who do not respond and those who initially respond but subsequently discontinue treatment, ESS is assumed to change immediately to the mean in the standard care group, reflecting the (regressed) mean position for a patient now receiving only standard care for their underlying OSA.

There are several differences between the company's and ERG's non-centred RTM analyses. Our version is subject to uncertainty over the rates of transition between the 'responder' and 'non-responder' status within the standard care and solriamfetol treatment arms. The company's pooling of these subgroups within the standard care arm is reasonable, given that there is no need to assess response to inform a treatment continuation decision. We also agree that, given the lack of long-term observational data on how ESS changes over time, the assumption that ESS remains stable except when patients discontinue solriamfetol is reasonable.

However, the assumption in the company's RTM model that non-responders to solriamfetol at 12 weeks achieve the same mean ESS (and hence utility) as the pooled population with standard care is more problematic. Trial data shows that non-responders to solriamfetol have a lower mean ESS at 12 weeks than the pooled standard care population (see Table 4 below). This translates to a mean utility score of approximately [redacted] for solriamfetol non-responders compared with [redacted] overall for standard care. We note that if we insert a utility of [redacted] for solriamfetol non-responders into the company's RTM model, solriamfetol is dominated by standard care. Hence, this assumption is a major source of uncertainty.

Table 4 ESS and utility estimates from different versions of the model

Treatment	Daily dose	% responders	Change from baseline ESS			Utility		
			Mean	Responders	Non-responders	Responders	Non-responders	
							Year 1	Year 2+
Company base case – placebo effect attributed to observation (Hawthorne)								
Standard care alone		0%	0.00	0.00	0.00	[redacted]	[redacted]	[redacted]
Standard care plus solriamfetol	37.5mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	75mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	150mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Company scenario – placebo effect attributed to true placebo								
Standard care alone		0%	0.00	0.00	0.00	[redacted]	[redacted]	[redacted]
Standard care plus solriamfetol	37.5mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	75mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	150mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Company scenario – placebo effect attributed to regression to the mean								
Standard care alone		NA	[redacted]	NA	NA			[redacted]
Standard care plus solriamfetol	37.5mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	75mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	150mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ERG 4-state model – placebo effect attributed to regression to the mean								
Standard care alone		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Standard care plus solriamfetol	37.5mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	75mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	150mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Source: Extracted from the company's models by the ERG
Bold text indicates an assumption rather than estimates derived from centred or uncentered TONES 3 data

3.4. Comment 4: Use of SF-6D data from the company's trials to assess quality of life

The NICE committee noted concerns over the sensitivity of the EQ-5D for people with OSA and concluded that mapping from the ESS to the EQ-5D may not adequately capture changes in quality of life (ACD 3.11). They also noted that the SF-6D can be more sensitive to this condition and requested SF-6D data from the company's trials (ACD 3.19).

However, the company has not provided this analysis. They reiterate arguments that neither the EQ-5D nor the SF-36 data collected in the TONES trials reflected the substantial burden of OSA on quality of life. The company also argues that although there was an immediate improvement in the vitality domain of the SF-36, this contributes little to the overall SF-6D utility score and that people are likely to take longer than 12 weeks to achieve substantial change on other domains. This latter argument is not supported by quality of life data from TONES 5, which did not show further improvement over 40 weeks of open label follow up (company's response to clarification question A11).

Furthermore, the contention that the SF-36 is insensitive to the impact of OSA on quality of life is not supported by the analysis of TONES 3 data. The paper by Weaver et al. (2020) is now in the public domain.[3] This reports significantly greater gains over 12 weeks in the 150 mg solriamfetol arm than in the placebo arm for five of the eight SF-36 subscales - vitality, role physical, social functioning, role emotional and general health (Figure 5, Weaver et al. 2020).[3] There were also trends suggestive of a dose response across the three licensed doses for the SF-36 PCS and MCS summary scores and vitality, role physical, social functioning and general health subscales.

The company cites comments from the ACD for pitolisant (ID1065) regarding the sensitivity of the EQ-5D and SF-6D at capturing quality of life in people with OSA and the committee's concerns over the use of a mapping algorithm (McDaid et al. 2009)[4], rather than direct trial data (Pitolisant ACD section 3.15, June 2021). The implication of the pitolisant committee's conclusion, if it were to be extended to the current solriamfetol appraisal, would be that direct EQ-5D results from TONES 3 should be used in the economic analysis. Under this approach, solriamfetol could not be cost-effective because EQ-5D utility results from TONES 3 showed only small changes from baseline and no meaningful difference between the solriamfetol dose groups and placebo.[3]

The SF-6D is not the NICE preferred utility measure, and there are ongoing debates around its validity and valuation.[5-7] However, we consider that there is some evidence that the SF-

6D may be more sensitive at detecting differences in quality of life for conditions with impacts on sleep than the EQ-5D (see section 4.2.7.2 of the ERG report). We also note that the SF-6D (original and revised versions) includes questions from four SF-36 domains for which some significant effects were detected in the analysis of TONES 3 data (vitality, role physical, role emotional and social functioning).[3]

ERG conclusion: We still believe that direct estimates of utility from the SF-6D applied to TONES 3 data would provide useful additional evidence to supplement the direct trial EQ-5D results and estimates from the NHWS ESS to EQ-5D mapping. Company scenarios with the McDaid ESS to EQ-5D mapped utilities may also provide useful additional scenarios. However, we consider that the company's time trade off (TTO) utility estimates are likely to be influenced by the high emphasis on daytime sleepiness in the health state descriptions and that the results are unlikely to be comparable to EQ-5D based utilities in other NICE appraisals.

3.5. Comment 5: Solriamfetol dose split

The company's revised base case (ACD sections 2.5.1) assumes a [redacted] dose split of solriamfetol 37.5 mg, 75 mg and 150 mg, reflecting US prescribing patterns. The base case and scenario analyses for alternative dose splits are reported in ACD sections 2.5.2 to 2.5.4. The resulting ICER estimates vary from [redacted] per QALY (40/40/20 dose split) to [redacted] per QALY (20/40/40).

3.6. Comment 6: Hospitalisation costs for serious adverse events

In the ERG model, hospitalisation costs were estimated based on rates of SAE-related hospital admissions for patients with OSA in TONES 5, with [redacted]% ([redacted]) of solriamfetol-treated patients hospitalised for SAEs. The company argued that only one such event was deemed treatment-related in TONES 5 (n=1 stroke [redacted] in the 150 mg arm), and that as TONES 5 was a single arm, open label extension study, the data do not demonstrate a difference between the intervention (solriamfetol) and comparator (placebo).

The company referred to a Periodic Safety Update Report (PSUR) for solriamfetol, where the number of adverse drug reactions in patients treated with solriamfetol in clinical practice is described as "relatively low". The company provided a copy of this report, at the request of the ERG. However, it does not include event counts or give an overall figure for the frequency of SAEs or hospitalisations due to SAEs in the clinical trial programme. For the post-marketing data, it gives some information on spontaneous reports of AEs and a

denominator estimate of exposure based on sales data, but these are not true measures of incidence.

At the request of the committee, the company include hospitalisation costs for the solriamfetol and placebo arms from the TONES 3 RCT in their revised base case analysis. They use rates of hospitalisation (shown in ACD response Table 15) calculated from all SAEs which led to hospitalisation in each trial arm of the TONES 3 RCT. Since TONES 3 was a 12-week study, observed rates were converted to an annualised rate. Under the [redacted] dose split assumption used in the company's base-case analyses, the proportion of solriamfetol patients hospitalised is assumed to be [redacted] versus [redacted] of placebo patients. We consider this to be highly unrealistic, given that in TONES 3 the active treatment (licensed doses only) had a higher rate of treatment related adverse events than placebo: [redacted] versus [redacted] (ERG report Table 22). Serious adverse events in TONES 3 were sparse and there were no treatment-related SAEs, this is not surprising given the sample size and short duration of this study.

The company has provided the following scenario analyses:

a) ERG preferred assumption: any SAE-related hospitalisation for solriamfetol from TONES 5 vs zero rate for SoC, with the ICER of [redacted] (ACD response Table 16)
b) Treatment-related SAE-related hospitalisation for solriamfetol from TONES 5 vs zero rate for SoC, with the ICER of [redacted] (ACD response Table 18)
c) Any SAE-related hospitalisation for solriamfetol from TONES 5 ([redacted]% of patients in the solriamfetol 150 mg arm and zero in other solriamfetol arms) vs Hospital Episodes Statistics (HES) rate for SoC ([redacted]% of patients with OSA hospitalised per year for reasons other than a sleep disorder), with the ICER of [redacted] (ACD response Table 17)

ERG conclusion: The company states that the ERG SAE-related hospital admission rate is a proxy for hospitalisations experienced in this population. In fact, we had intended this more as a proxy for wider treatment-related adverse events, which did not incur any disutility or treatment cost (beyond a GP consultation or treatment discontinuation) in the company's original base case. We therefore believe that the ERG's analysis (scenario a above) is justified. Scenario b (including costs for the SAE-related hospitalization for stroke in TONES 5) would also be reasonable, although we note that the unit cost attributed to this event in the model (£3,645, the HRG cost for sleep disorder) is much lower than the health and social care cost associated with a stroke. We consider that the company's revised base case and scenario c, with a higher rate of hospitalization with standard care than with solriamfetol, are implausible.

3.7. Comment 7: Potential impact on increased monitoring of adherence to CPAP

The ERG does not have any comment to make on this issue.

3.8. Comment 8: Partner utilities

The company repeat scenario analyses considering impact of EDS on partner's quality of life, based on the relationship between patient and partner utilities estimated from the time trade off (TTO) exercise (ACD response Tables 19-21).

The ERG provided a critique of the TTO in section 4.2.7.2 of our report. We concluded that we do not favour use of the TTO utility estimates, as the health state descriptions place a very high emphasis on daytime sleepiness, so the results are unlikely to be comparable with utility values in other NICE appraisals derived from the EQ-5D. We therefore consider that there is high uncertainty over the relationship between partner and patient utilities estimated from the TTO analysis.

3.9. Comment 9: Treatment in secondary care

The ERG does not have any comment to make on this issue.

3.10. Comment 10: Other issues

In section 2.10.4 of the company's ACD response, the company represent data from their response to technical engagement, which they argue provides "strong evidence that the placebo effect observed in TONES 3 is not regression to the mean". This provides useful commentary.

4. References

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

Solriamfetol for treating excessive waketime sleepiness caused by obstructive sleep apnoea

Evidence Review Group's critique of the company's response to the appraisal consultation document: ADDENDUM (September 2021)

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Academic in confidence (AIC) information in yellow

1. Introduction

The ERG has run some additional scenarios to test the combined effect of three key uncertainties that remain after the company's response to the ACD.

1.1. Costs for hospital admissions related to adverse events

The company use data from the 12-week TONES 3 trial in their base case: with estimated annual incidence of [redacted], [redacted] and [redacted] respectively for the 37.5 mg, 75 mg and 150 mg solriamfetol doses; and [redacted] for the placebo arm. (Note, these numbers are taken from the company's submitted base case model and differ slightly from those reported in ACD response Table 15).

The ERG preferred analysis in our original report used estimates from the TONES 5 open label study: [redacted] per year for serious adverse event (SAE) related hospital admissions for patients on the solriamfetol 150 mg dose and 0% for other licensed doses, and by assumption 0% per year for standard care. In their ACD response, the company presents another scenario based on treatment-related admissions in TONES 5, which suggests a lower rate of [redacted] per year for the 150 mg solriamfetol dose. We agree that this is reasonable.

1.2. The source of utility estimates

There is uncertainty over the utilities because there were no consistent differences in EQ-5D utility scores between treatment arms in the TONES 3 trial. The company did not provide SF-6D utility estimates from the trial, which we believe might have been more sensitive to the effect of sleep.

The company base case uses utility estimates from a new mapping algorithm that estimated the relationship between improvements in sleep (ESS reductions) and EQ-5D utilities, using data from the National Health and Wellness Survey (NHWS). They also provide scenarios with a published mapping algorithm from ESS to EQ-5D, developed by McDaid and colleagues for the NICE appraisal of continuous positive airway pressure for obstructive sleep apnoea (TA139). Other scenarios include utilities elicited from members of the public by a time trade off (TTO) with health state vignettes.

The ERG considers that the NHWS mapping algorithm was well conducted and reported, though we have some concerns that the sample may have been subject to recruitment bias due to the use of an online sample with self-reporting of diagnosis. In

the absence of trial data, the McDaid algorithm provides an alternative, more conservative scenario for utility estimation.

1.3. Placebo mechanisms

There are three potential mechanisms that may explain the effect in the TONES 3 placebo arm: observation ('Hawthorne'); regression to the mean (RTM); and 'true placebo'. The company assume an observation mechanism in their base case, by adjusting trial results for both solriamfetol and placebo arms (centring). They argue that this is conservative, as there is evidence to support a true placebo explanation and against regression to the mean. In response to a committee request, the company developed an RTM version of their model and presented a threshold analysis with varying contributions from the three mechanisms.

The ERG considers that it is likely that all three mechanisms contributed to the trial results, but that it is difficult to quantify these contributions. We have concerns that the company's RTM model under-estimates ICERs because of the assumption that non-responders to solriamfetol at 12 weeks would attain the same ESS (and hence utility) as the mean for all patients in the placebo arm.

2. Description of additional scenarios

Table 1 below shows three sets of additional scenarios to further explore the combined effects of the above uncertainties.

The first two sets of scenarios include hospitalisation costs based on TONES 5, with all other assumptions as in the company's revised base case. The third set of scenarios adds a change to the source of utility estimates (the McDaid algorithm) to scenario 2. For each scenario set we present four combinations of the placebo mechanisms.

The ERG prefers scenario set 1c with hospitalisation costs estimated from treatment-related admissions in TONES 5, the NHWS utility mapping, and an equal contribution of the three placebo mechanisms. However, we note that uncertainty remains high due to the lack of direct evidence of an effect on utility from the trial and the difficulty in quantifying the relative contributions of the three potential causes of the placebo effect.

Table 1 ERG scenarios: PAS for solriamfetol

			Total		Incremental		ICER
Placebo mechanism		Treatment	Costs	QALYs	Costs	QALYs	£ / QALY
Company's revised base case							
100% Observation		SC alone	£4,810	11.524			
		SC + Sol	[redacted]	11.969	[redacted]	0.445	[redacted]
Scenario 1: TONES 5 hospitalisations (Sol 150 mg [redacted]							
1a	100% Observation	SC alone	£0	11.524			
		SC + Sol	[redacted]	11.969	[redacted]	0.445	[redacted]
1b	25% RTM 50% Observation 25% True placebo	SC alone	£0	11.743			
		SC + Sol	[redacted]	12.212	[redacted]	0.470	[redacted]
1c	33% RTM 33% Observation 33% True placebo	SC alone	£0	11.816			
		SC + Sol	[redacted]	12.294	[redacted]	0.478	[redacted]
1d	50% RTM 25% Observation 25% True placebo	SC alone	£0	11.962			
		SC + Sol	[redacted]	12.393	[redacted]	0.431	[redacted]
Scenario 2: TONES 5 hospitalisations (Sol 150 mg [redacted]							
2a	100% Observation	SC alone	£0	11.524			
		SC + Sol	[redacted]	11.969	[redacted]	0.445	[redacted]
2b	25% RTM 50% Observation 25% True placebo	SC alone	£0	11.743			
		SC + Sol	[redacted]	12.212	[redacted]	0.470	[redacted]
2c	33% RTM 33% Observation 33% True placebo	SC alone	£0	11.816			
		SC + Sol	[redacted]	12.294	[redacted]	0.478	[redacted]
2d	50% RTM 25% Observation 25% True placebo	SC alone	£0	11.962			
		SC + Sol	[redacted]	12.393	[redacted]	0.431	[redacted]
Scenario 3: TONES 5 hospitalisations (Sol 150 mg [redacted] & McDaid utilities							
3a	100% Observation	SC alone	£0	13.963			
		SC + Sol	[redacted]	14.346	[redacted]	0.383	[redacted]
3b	25% RTM 50% Observation 25% True placebo	SC alone	£0	14.123			
		SC + Sol	[redacted]	14.566	[redacted]	0.443	[redacted]
3c	33% RTM 33% Observation 33% True placebo	SC alone	£0	14.176			
		SC + Sol	[redacted]	14.639	[redacted]	0.463	[redacted]
3d	50% RTM 25% Observation 25% True placebo	SC alone	£0	14.282			
		SC + Sol	[redacted]	14.718	[redacted]	0.436	[redacted]

Source: Company's ACD response, checked by the ERG using submitted models dated 09/08/21
Abbreviations: SC standard care; Sol solriamfetol; PAS patient access scheme.

Additional analysis to address uncertainty in TONES 3 EQ-5D trial data

Jazz maintains their position that the trial EQ-5D is inappropriate for use in the economic modelling for ID1499, for the reasons previously described in the submission. However, in light of the Committee's suggested approach of combining trial EQ-5D and McDaid EQ-5D, and given the need to adopt an approach that addresses the uncertainties surrounding utilities, Jazz have conducted a further analysis of the TONES 3 trial EQ-5D that may be helpful in resolving these issues.

As discussed throughout the NICE process, there are substantial limitations with the trial EQ-5D, including the ceiling effect and face validity of the utilities in the trial due to the high baseline EQ-5D. In the TONES 3, the mean baseline utility in the overall population was [redacted], indicating that there was limited room for patients to achieve a utility gain in response to treatment. Given the widely accepted and acknowledged burden of EDS, the baseline values are inconsistent with the utility profile that would be expected in this patient population. However, in the overall TONES 3 population [redacted]% of patients had a baseline utility value of 1 and this increased at week 12 to [redacted]%. This indicated that reducing the ceiling effect may have allowed a greater improvement in EQ-5D than was possible in the trial. Jazz thus investigated the impact on EQ-5D scores of reducing this ceiling effect in the TONES 3 data.

1. Splitting EQ-5D by ESS response

To maintain consistency with the current model, this new analysis includes patients with ESS>12 (per the Committee's agreed population for the analysis). Using TONES 3 data, patients treated with solriamfetol were subdivided into those *with* versus *without* an ESS improvement of ≥2 points (per the Committee's preferred response definition). This generated the data shown in Table 1. Although these utility values are lower than would be predicted by either the NHWS or McDaid, the data should be considered in the context of limitations of the trial EQ-5D as previously described.

Table 1. Utility values for responders and non-responders to solriamfetol in TONES 3 (ESS >12) using trial data

	Mean baseline EQ-5D	Mean Wk 12 EQ-5D	Difference
Responders	[redacted]	[redacted]	[redacted]
Non-responders	[redacted]	[redacted]	[redacted]

2. Equivalent utility improvement predicted by the model using NHWS/McDaid

For context against the mapping algorithms, the equivalent utility improvements that would be achieved in these patients based on trial EQ-5D and predicted by the model are shown in Table 2. The ceiling effect means that due to high baseline utility scores, there is minimal room for utility scores to improve during the trial; the impact of the ceiling effect has been described previously (Feng, 2021; Nolan CM, 2016).

Table 2. Equivalent utility value predictions for TONES 3 trial data based on NHWS/McDaid

		Mean baseline EQ-5D	Mean Wk 12 EQ-5D	Difference
NHWS	Responders	[redacted]	[redacted]	[redacted]
	Non-responders	[redacted]	[redacted]	[redacted]
McDaid	Responders	[redacted]	[redacted]	[redacted]
	Non-responders	[redacted]	[redacted]	[redacted]

3. Impact of the ceiling effect

Of the many limitations of the trial EQ-5D data described throughout the company submission, the ceiling effect appears to be one of the largest. Jazz carried out an exploratory analysis to understand the potential improvement in utility that could be achieved by accounting for the ceiling effect.

To conduct this analysis, Jazz initially considered a simple truncation of the dataset, e.g. excluding all patients with a baseline utility above a given value. However, this form of truncation would likely bias the analysis because it is reasonable to expect *some* patients will report a baseline utility of 1 in almost every dataset assessing EQ-5D. For example, in a study on chronic obstructive pulmonary disease, between 6% and 11% of patients reported a utility index of 1 both before and after treatment, and 3% to 4% of patients reported an EQ-VAS score of 100 before and after treatment (Nolan CM, 2016).

Therefore, rather than truncating the data, the current analysis drew multiple random samples from the TONES 3 data, using each sample to generate a mean baseline and week 12 EQ-5D value. This allowed for a wide range of individual patient utility values (including patients with high baseline mean EQ-5D) to be preserved whilst generating mean utility values per sample; a subset of these values was below the baseline value observed in TONES 3 and more representative of baseline values found in previous literature. In the subsets where sampled mean values were lower than those observed in TONES 3, the changes in utility values from baseline to week 12, were explored in an attempt to understand the potential impact of ceiling effects. This may be considered a simplistic approach to exploring the potential impact of a reduction in ceiling effect, as opposed to confirmation of the impact of reduced ceiling effect on utility values.

A challenge with this type of analysis was the number of patients from the TONES 3 data to include in each simulated sample: too few would make each sample unstable, whereas too many would generate values at a higher range of utility (i.e. as the baseline utility values in TONES 3 were high, the mean of a large sample of these patients would also be high). For example, using 50% of the patients in TONES 3 for each sample would generate a minimum mean baseline utility of 0.759 (the mean of the lowest baseline utilities in the trial).

For this analysis, a total of ten patients was believed to be the minimum required for each simulation, thus for each sample, data for 10 randomly selected patients from TONES 3 were used. Although this restricts the ability to explore lower baseline EQ-5D values due to the frequency of low baseline values observed in TONES 3, given the challenges of this type of analysis, 10 was believed to be a reasonable pool from which to draw sample data. Due to the small number of patients per sample, the number of simulations was increased to 100,000 (vs the originally intended 10,000) in order to generate a range of means more representative of mean values found in previous literature.

Across the 100,000 simulations, all simulations with a baseline utility score of 0.005 points higher or lower than the published baseline values from previous CPAP studies in this therapy area were averaged to demonstrate what might have happened to the week 12 utilities in the TONES 3 trial had the trial mean baseline utilities been similar to those in the previous studies.

The results of the analysis (Table 3) indicate that the utility values suggested by NHWS and McDaid in the economic model (Table 2) are reasonable estimates. The results shown describe the change in utility values for Responders and Non-Responders over 12 weeks of TONES 3 had the mean baseline utility been similar to each prior study. For example, in the row “Mar 2003” if Responders in TONES 3 had a mean baseline utility of 0.74 instead of 0.838, their EQ-5D improvement would have been approximately 0.072 instead of 0.034, which is not dissimilar to the scores predicted for Responders using the NHWS in the economic model.

Table 3. Utility values predicted using an assumed baseline utility from alternative studies in OSA

Study whose baseline we attempted to simulate in TONES 3		Baseline EQ-5D in reference study	Responders*				Non-responders*			
			Mean ESS improvement in TONES 3	Simulated Baseline EQ-5D†	Wk 12 EQ-5D in TONES 3	Difference	Mean ESS improvement in TONES 3	Simulated Baseline EQ-5D†	Wk 12 EQ-5D in TONES 3	Difference
Jenkinson 1997/1998	CPAP	0.79	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Chakravorty 2002	CPAP	0.73	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Lifestyle advice	0.77	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Mar 2003	CPAP	0.74	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
McMillan 2014	CPAP	0.666	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	BSC	0.668	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

* Values for responders and non-responders based on sampled generated as described above.

† Simulated baselines were generated using the sampling process described above.

‡ Note that in this study, the lowest 15 values were selected.

§ Note that in this study, the lowest 150 values were selected to match responders as closely as possible.

Addendum

In response to Table 1 above, the NICE Technical Team requested similar information from TONES 3 for the placebo only arm, and overall population using solriamfetol/placebo pooled data (for patients with ESS>12 at baseline, per the Committee's preferred assumption). This requested information is provided in Table 4. The data shown in Table 1 above were provided to highlight the limitations of the trial EQ5D, and consequently the data provided in Table 4 cannot be used to endorse any numerical differences between the solriamfetol and placebo groups.

The analysis above indicates that the McDaid & NHWS mapped values reflect the plausible change in quality of life that a patient may experience over time, following an improvement in their EDS due to solriamfetol treatment. Furthermore, in both ID1499 (the current appraisal, in OSA) and ID1602 (the Narcolepsy appraisal for solriamfetol) the Committee concluded that mapping from the ESS to the EQ-5D may not adequately capture the impact of treatment on improving quality of life and the ERG concluded that the mapping may underestimate the impact of treatments on the quality of life in this condition. The Committee also concluded that partner utility values are important to consider, but the NHWS/McDaid algorithms do not incorporate partner utilities, therefore there may be further utility gains due to solriamfetol treatment than captured in this analysis.

Jazz are reluctant to combine EQ-5D utility change scores for pooled solriamfetol and placebo responders with utilities derived via the McDaid or NHWS algorithms given the differing approaches to capturing treatment effect on utility, and the potential underestimation of quality of life changes. Assigning utility values based on a treatment agnostic responder/non-responder definition, as would be the case with pooled solriamfetol and placebo EQ-5D values, does not take differential treatment effect between arms into account, and would therefore conflict with the approach using the McDaid and NHWS algorithms which derive utility values as a function of ESS score, and thus treatment effect by arm. Furthermore, any such analysis does not account for the fact that patients are not prescribed placebo in practice.

Table 4. Utility values for responders and non-responders to placebo, solriamfetol, and overall population in TONES 3 (ESS >12) using trial data

Arm	Response Strata†	Mean EQ-5D at baseline	Mean EQ-5D at week 12	Mean change in EQ5D
Solriamfetol	Responder	[redacted]	[redacted]	[redacted]
	Non-responder	[redacted]	[redacted]	[redacted]
Placebo	Responder	[redacted]	[redacted]	[redacted]
	Non-responder	[redacted]	[redacted]	[redacted]
Pooled placebo and solriamfetol	Responder	[redacted]	[redacted]	[redacted]
	Non-responder	[redacted]	[redacted]	[redacted]

† Response defined as ESS reduction of ≥2 points from baseline to week 12 per the Committee's preferred assumption.
Data reflect the unadjusted raw individual patient-level data from TONES 3.
Patients without any post-baseline EQ-5D scores were excluded from the analysis. Last observation carried forward was applied to any patients with ≥ 1 post-baseline EQ-5D score but who did not have a full set of post-baseline EQ-5D values.

References

Feng, Y. K. (2021). Psychometric properties of the EQ-5D-5L: a systematic review of the literature. *Qual Life Res, 30*, 647-673. doi:10.1007/s11136-020-02688-y

Nolan CM, L. L. (2016). The EQ-5D-5L health status questionnaire in COPD: validity, responsiveness and minimum important difference. *Thorax, 71*, 493-500.

Solriamfetol OSA (ID1499)

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

Solriamfetol for treating excessive waketime sleepiness caused by obstructive sleep apnoea

Evidence Review Group's critique of the company's response to the appraisal consultation document: Additional analysis (September 2021)

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1. Introduction

Following the NICE Appraisal Committee meeting on 14 Sept 2021, the ERG was asked to run some additional scenarios. The committee was interested to see ICERs using the following assumptions:

- Hospitalisation rates based on treatment related SAE from TONES 5 (scenario 3 on slide 24 of the committee slides): [redacted] per year for 150 mg solriamfetol; 0% for other solriamfetol doses and standard care alone.
- Utility gain for solriamfetol derived from the average of EQ-5D utility gain from TONES 3 and the utility gain from McDaid ESS to EQ-5D utility mapping.
- Two placebo effect scenarios: 100% observation bias (Hawthorne effect) and an equal mixture of the 3 mechanisms.
- Other assumptions as in the base case (as specified in the company's ACD response, dated 25/06/21).

The company has submitted three versions of their model (dated 09/08/21), to reflect different assumptions about the placebo mechanisms: Hawthorne, true placebo and regression to the mean (RTM). We adapted these three models to include TONES 3 EQ-5D results as an alternative source of utilities. This required some assumptions because EQ-5D results from the trial have not been reported separately as a function of ESS or response.

2. ERG assumptions for extrapolation of trial EQ-5D utilities

TONES 3 EQ-5D results are summarised in Table 1. These utilities are consistent with the NICE reference case: EQ-5D-5L is valued with the van Hout crosswalk method and UK value set. The differences in utility gain between the study arms are not statistically significant.

Table 1 TONES 3 EQ-5D-5L utility results (mITT Population)

	Placebo	Solriamfetol 37.5 mg	Solriamfetol 75 mg	Solriamfetol 150 mg
Number of patients	n=114	n=56	n=58	n=116
Mean baseline utility	[redacted]	[redacted]	[redacted]	[redacted]
Mean utility gain from baseline to week 12 (SE)	0.02 (0.009)	0.01 (0.012)	0.02 (0.012)	0.03 (0.008)
Mean difference in utility gain (95% CI)		-0.01 (-0.04, 0.02)	0.00 (-0.03, 0.03)	0.01 (-0.02, 0.03)

Source: Weaver et al. 2020 supplementary appendix Table E1. Baseline scores from TONES 3 Clinical Study Report Table 14.2.10.1

For the trial EQ-5D scenarios, we assumed a mean baseline utility of 0.85, which is similar to the general population utility (mean age 54, 60% male). The ICER is not sensitive to the absolute utility values, as they cancel out in the incremental QALY calculation. Modelled changes in utility during the initial 12-week induction period and subsequently depend on the assumed cause of placebo effects. The assumptions underlying the three placebo mechanisms and how they can be corrected for are summarised in committee slide number 11. We applied these principles to include EQ-5D trial data, as in Table 2.

Table 2 Utility estimates based on TONES 3 EQ-5D analysis

	Mean utility gain 0-12 weeks	Responders		Non-responders	
		Year 1	Year 2+	Year 1	Year 2+
Regression to the mean (no adjustment to placebo or solriamfetol)					
Placebo	0.02	0.8698	0.8700	0.8700	0.8700
Solriamfetol 37.5mg	0.01	0.8599	0.8600	0.8677	0.8700
Solriamfetol 75mg	0.02	0.8698	0.8700	0.8700	0.8700
Solriamfetol 150mg	0.03	0.8797	0.8800	0.8723	0.8700
Hawthorne model (placebo and solriamfetol centred)					
Placebo	0.00	0.8500	0.8500	0.8500	0.8500
Solriamfetol 37.5mg	-0.01	0.8401	0.8400	0.8477	0.8500
Solriamfetol 75mg	0.00	0.8500	0.8500	0.8500	0.8500
Solriamfetol 150mg	0.01	0.8599	0.8600	0.8523	0.8500
True placebo (no effect for placebo, solriamfetol as observed in the trial)					
Placebo	0.00	0.8500	0.8500	0.8500	0.8500
Solriamfetol 37.5mg	0.01	0.8599	0.8600	0.8523	0.8500
Solriamfetol 75mg	0.02	0.8698	0.8700	0.8546	0.8500
Solriamfetol 150mg	0.03	0.8797	0.8800	0.8569	0.8500

Source: ERG estimates based on trial results (see Table 1) and placebo assumptions

EQ-5D results from the trial are not available separately for ESS responders and non-responders at 12 weeks, in these scenarios the overall mean utility gain is used for both groups while on the same treatment. However, ESS response is still used to model solriamfetol continuation after induction. The differences between year 1 and year 2 utility estimates are due to the company's base case assumptions about the speed of ESS change (and hence utility change) during the induction period: for responders, ESS change is assumed to occur within one week, and is then maintained until treatment discontinuation or death: for non-responders, the week 12 change in ESS is applied throughout the induction period. After treatment cessation, patients revert to the baseline value, except under the regression to the mean assumption.

The results below are all deterministic, as the PSA did not work in the company's submitted versions of the true placebo or regression to the mean models (an error was returned for QALYs in simulations).

2.1. Scenario analysis results

Table 3 ERG scenarios: deterministic with PAS for solriamfetol

Placebo mechanism		Treatment	Total		Incremental		ICER
			Costs	QALYs	Costs	QALYs	£ / QALY
Base case		SC alone	£4,810	11.524			
		SC + Sol	[redacted]	11.969	[redacted]	0.445	[redacted]
TONES 5 TRSAE hospital costs		SC alone	£0	11.524			
		SC + Sol	[redacted]	11.969	[redacted]	0.445	[redacted]
Hawthorne model: with TONES 5 TR SAE hospital costs							
4a	McDaid utilities	SC alone	£0	13.963			
		SC + Sol	[redacted]	14.346	[redacted]	0.383	[redacted]
4b	EQ-5D from trial	SC alone	£0	15.202			
		SC + Sol	[redacted]	15.216	[redacted]	0.014	[redacted]
4c	50% McDaid / 50% trial EQ-5D	SC alone	£0	14.582			
		SC + Sol	[redacted]	14.781	[redacted]	0.198	[redacted]
True placebo model: with TONES 5 TRSAE hospital costs							
5a	McDaid utilities	SC alone	£0	13.963			
		SC + Sol	[redacted]	14.615	[redacted]	0.652	[redacted]
5b	EQ-5D from trial	SC alone	£0	15.202			
		SC + Sol	[redacted]	15.377	[redacted]	0.175	[redacted]
5c	50% McDaid / 50% trial EQ-5D	SC alone	£0	14.582			
		SC + Sol	[redacted]	14.996	[redacted]	0.414	[redacted]
Company RTM model: with TONES 5 TRSAE hospital costs							
6a	McDaid utilities	SC alone	£0	14.601			
		SC + Sol	[redacted]	14.956	[redacted]	0.355	[redacted]
6b	EQ-5D from trial	SC alone	£0	15.560			
		SC + Sol	[redacted]	15.570	[redacted]	0.010	[redacted]
6c	50% McDaid / 50% trial EQ-5D	SC alone	£0	15.081			
		SC + Sol	[redacted]	15.263	[redacted]	0.182	[redacted]
Equal mix of models: with TONES 5 TRSAE hospital costs							
7a	McDaid utilities	SC alone	£0	14.176			
		SC + Sol	[redacted]	14.639	[redacted]	0.463	[redacted]
7b	EQ-5D from trial	SC alone	£0	15.321			
		SC + Sol	[redacted]	15.387	[redacted]	0.066	[redacted]
7c	50% McDaid / 50% trial EQ-5D	SC alone	£0	14.748			
		SC + Sol	[redacted]	15.013	[redacted]	0.265	[redacted]

Source: ERG adapted version of the company's submitted models dated 09/08/21

Abbreviations: SC standard care; Sol solriamfetol; TRSAE treatment-related serious adverse events; PAS patient access scheme.

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

Solriamfetol for treating excessive waketime sleepiness caused by obstructive sleep apnoea

Evidence Review Group's critique of the company's response to the appraisal consultation document: Additional analysis (26 Sept 2021)

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Date completed	26 September 2021

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1.1. Scenario analysis results

Table 1 ERG scenarios: deterministic with PAS for solriamfetol

Placebo mechanism		Treatment	Total		Incremental		ICER
			Costs	QALYs	Costs	QALYs	£ / QALY
Base case		SC alone	£4,810	11.524			
		SC + Sol	[redacted]	11.969	[redacted]	0.445	[redacted]
Using primary OSA therapy at baseline		SC alone	£4,811	11.575			
		SC + Sol	[redacted]	11.991	[redacted]	0.415	[redacted]
Not using primary OSA therapy at baseline		SC alone	£4,810	11.373			
		SC + Sol	[redacted]	11.893	[redacted]	0.521	[redacted]
Hawthorne model: with TONES 5 TR SAE hospital costs							
4c	50% McDaid / 50% trial EQ-5D	SC alone	£0	14.582			
		SC + Sol	[redacted]	14.781	[redacted]	0.198	[redacted]
4ci	Using primary OSA therapy	SC alone	£0	14.596			
		SC + Sol	[redacted]	14.777	[redacted]	0.181	[redacted]
4cii	Not using primary OSA therapy	SC alone	£0	14.544			
		SC + Sol	[redacted]	14.782	[redacted]	0.238	[redacted]
Equal mix of models: with TONES 5 TR SAE hospital costs							
7c	50% McDaid / 50% trial EQ-5D	SC alone	£0	14.748			
		SC + Sol	[redacted]	15.013	[redacted]	0.265	[redacted]
7ci	Using primary OSA therapy	SC alone	£0	14.763			
		SC + Sol	[redacted]	15.038	[redacted]	0.275	[redacted]
7cii	Not using primary OSA therapy	SC alone	£0	14.732			
		SC + Sol	[redacted]	15.060	[redacted]	0.328	[redacted]

Source: ERG adapted version of the company's submitted models dated 09/08/21

Abbreviations: SC standard care; Sol solriamfetol; TRSAE treatment-related serious adverse events; PAS patient access scheme.

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

Solriamfetol for treating excessive waketime sleepiness caused by obstructive sleep apnoea

Evidence Review Group's critique of the company's response to the appraisal consultation document: Additional analysis (7 October 2021)

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1.1. Scenario analysis results

Following the appraisal committee meeting on 14 September 2021, NICE asked the ERG to run some additional scenarios (Table 1).

These scenarios include the company's post-ACD2 revised base case assumptions with:

- Costs for hospital admissions for treatment related serious adverse events
- Utilities based on a combination of the McDaid algorithm and EQ-5D results from the TONES 3 clinical trial
- Adjustment for the placebo effects in the company's 'Hawthorne' version of the model, and an equal combination of the Hawthorne model with the 'true placebo' and 'regression to the mean (RTM)' models
- And subgroup analysis for people who were/were not using primary OSA therapy at baseline

Six new scenarios use McDaid utility mapping with the coefficient for the change in EQ-5D utility per unit increase in ESS (-0.0096984) adjusted for the estimated relationship between these variables in the TONES 3 trial [redacted]). Taking the mean of these two values, an estimated coefficient of [redacted] is obtained. The method of calculation for this estimate is shown in cells U22 to Y32 on the 'efficacy' sheets of the three versions of the company's model edited by the ERG. These edited models are submitted with this addendum, together with a 'Combination' model to link results from these three models.

ERG edits to the company's models are highlighted in green. The 'Results' sheet includes controls to run all of the scenarios. In order to run the RTM analysis for the subgroups, we had to edit the '_IPD_OSA_Summary' sheets for these analyses to include the company's assumptions. The RTM model also includes an option to test alternative ERG assumptions for the utility of people without an initial response to solriamfetol or who stop treatment due to loss of effect or adverse events (based on the mean for solriamfetol non-responders, rather than the mean for all patients in the standard care arm as in the company's RTM model). We don't present results from this analysis but note that it shows high uncertainty over the QALY gain, and hence ICER for solriamfetol.

Table 1 ERG scenarios: deterministic with PAS for solriamfetol

Placebo mechanism		Treatment	Total		Incremental		ICER
			Costs	QALYs	Costs	QALYs	£ / QALY
Base case		SC alone	£4,810	11.524			
		SC + Sol	[redacted]	11.969	[redacted]	0.445	[redacted]
Using primary OSA therapy at baseline		SC alone	£4,811	11.575			
		SC + Sol	[redacted]	11.991	[redacted]	0.415	[redacted]
Not using primary OSA therapy at baseline		SC alone	£4,810	11.373			
		SC + Sol	[redacted]	11.893	[redacted]	0.521	[redacted]
Hawthorne model: with TONES 5 TR SAE hospital costs							
4c	50% McDaid / 50% trial EQ-5D	SC alone	£0	14.761			
		SC + Sol	[redacted]	15.037	[redacted]	0.277	[redacted]
4ci	Using primary OSA therapy	SC alone	£0	14.776			
		SC + Sol	[redacted]	15.028	[redacted]	0.252	[redacted]
4cii	Not using primary OSA therapy	SC alone	£0	14.715			
		SC + Sol	[redacted]	15.047	[redacted]	0.332	[redacted]
Equal mix of models: with TONES 5 TR SAE hospital costs							
7c	50% McDaid / 50% trial EQ-5D	SC alone	£0	14.914			
		SC + Sol	[redacted]	15.249	[redacted]	0.335	[redacted]
7ci	Using primary OSA therapy	SC alone	£0	14.920			
		SC + Sol	[redacted]	15.234	[redacted]	0.314	[redacted]
7cii	Not using primary OSA therapy	SC alone	£0	14.897			
		SC + Sol	[redacted]	15.277	[redacted]	0.381	[redacted]

Source: ERG adapted version of the company's submitted models dated 09/08/21

Abbreviations: SC standard care; Sol solriamfetol; TRSAE treatment-related serious adverse events; PAS patient access scheme.

Response

Overview

Jazz appreciates the ERG's critique of the exploratory analysis provided to NICE regarding the potential impact of ceiling effects on EQ-5D in the TONES 3 trial. Jazz would like to emphasise that the analysis was performed on an exploratory basis in the absence of other sources of data, however Jazz agrees with the limitations of this analysis described by the ERG. Jazz did not anticipate that the utility values presented in this analysis would be used in the economic model nor was the analysis intended to form a base case analysis. Rather the analysis intended to provide a new perspective with which to approach the trial utility data, by illustrating the potential impact that a reduced ceiling effect, more in line with other OSA studies, may have had on the trial EQ-5D values. For the reasons previously described in Form B.3.4 and in the company's response to both Technical Engagement and ACD, Jazz's position remains that the trial EQ5D data are inappropriate for use in the model, and consequently, Jazz do not agree with the blended utility methodology combining the trial EQ-5D data with McDaid. Jazz's position is that the NHWS analysis is a more suitable and representative dataset in this indication (patients with EDS due to OSA despite use of their primary OSA therapy).

Section 2 ERG Critique of company analysis of EQ-5D ceiling effect

With reference to the ERG's critique *"We note that although these two cited papers warned about the potential impact of high utility scores from the EQ-5D-5L on responsiveness, they both reached favourable conclusions about the psychometric properties of the EQ-5D-5L and neither suggested statistical manipulation such as discarding or selectively sampling data to avoid or reduce the problem"* Jazz agrees with this statement but note that there was no expectation that either paper would suggest analytical methods aimed at overcoming ceiling effect given their research designs (a systematic literature review and a psychometric evaluation). As such, the absence of proposed methodology in these papers should not be considered evidence of inappropriate methodology.

Although the systematic literature review by Fang et al (2021) reached favourable conclusions about the psychometric properties of the EQ-5D-5L across a broad range of populations, it is important to note that the study concluded *"The EQ-5D-5L is a reliable and valid generic instrument that describes health status which can be applied to a broad range of populations and settings. The assessment of responsiveness, in particular, needs further and more rigorous exploration. Rather large ceilings persist in general population samples, reflecting the conceptualization of the EQ-5D instrument, which focuses on limitations in function and symptoms, and does not include positive aspects of health such as energy or well-being."* This conclusion is particularly important within the context of EDS due to OSA, which may commonly be associated with 'energy.' Given this conclusion, Jazz believe it is important that these potential limitations specific to the OSA population are fully considered when examining this issue.

The ERG questioned whether Jazz used the correct baseline EQ-5D values from the literature (as used in the exploratory analysis) given that the baseline values applied reflected values prior to the initiation of CPAP. However, Jazz believes that the baseline utility values in these studies are more appropriate describe the target population for solriamfetol than the post treatment utility values. Solriamfetol is indicated for patients with EDS due to OSA who *have not* been satisfactorily managed using a primary OSA therapy, therefore, it is unlikely that patients eligible for solriamfetol would have achieved the maximum gain in utility from their primary OSA therapy as their symptom of EDS

persisted post treatment. As such, the posttreatment values in the literature would overestimate the utility in patients with residual EDS despite primary OSA therapy. However, Jazz acknowledges the limitations of the utility values used and emphasise that there is a distinct lack of published quantitative evidence specifically reporting on EDS due to OSA despite use of a primary OSA therapy.

Jazz further note that the ERG suggests the ceiling effects observed in the trial would be similar to those found in the previous literature. However, these studies do not provide the granularity of data to determine if this is the case, and Jazz are unaware of studies that report this form of data, therefore it is unknown whether ceiling effect contributed towards the outcome in these studies. Notwithstanding this, the literature values are lower than those in TONES 3, suggesting that the ceiling effect is likely to be less of a factor for these studies than is the case in the TONES 3 data. Jazz maintains their position that the EQ-5D values from the TONES 3 trial lack face validity (as described in Section 3.4 of Form B in the original company submission). Further, as illustrated by the lack of the relationship between ESS and EQ-5D in the trial data, and contrary to the approach accepted in NICE TA139, the trial values would be expected to differ from those collected in previous studies.

Jazz would like to emphasise again that this exploratory analysis aimed to provide insight into the potential impact that the observed ceiling effect might have had on the utility data, rather than a methodologically validated approach, and Jazz thus agree with the ERG that the exploratory approach has limitations.

Section 3 Commentary on additional EQ-5D information provided by the company

Regarding the inconsistency in solriamfetol responder utility values, Jazz confirms that the ERG is correct in that the value should be .834 (rather than .838), this was a typographical error.

The 300 mg dose of solriamfetol is unlicensed and therefore has been excluded from the company submission throughout the ID1499 process, except in situations where 300 mg data was required to describe the TONES trial study designs. Clinical and cost-effectiveness data have always excluded the 300 mg dose, and Jazz confirms that as per the company submission, data for the 300 mg dose of solriamfetol were similarly excluded from the analysis presented.

With regards the ERGs comment that "*It is not stated if the reported EQ-5D-5L index values (utilities) are calculated using the NICE preferred method, with the van Hout crosswalk procedure using the UK EQ-5D-3L value set. A footnote to Table 14.2.10.1 in the clinical study report for TONES 3 states: "Values from UK are used if the country is not available". This implies that other value sets were used for patients from other countries*." The company's base case analysis used utility values from the NHWS analysis. As described in the company's response to Technical Engagement (Key Issue 5), in the original company model, the NHWS analysis used country-specific utility value for each patient. At Technical Engagement stage, the company provided an updated NHWS analysis mapped using the UK value set and applied this updated version in the company updated cost-effectiveness analysis. As confirmed at TE stage, the NHWS mapping was completed in line with NICE DSU guidelines.

Regarding the analysis provided, as outlined in the Addendum to the analysis provided, Jazz initially only provided Table 1, which focused on solriamfetol responders and non-responders. However, the NICE technical team then requested Table 4 (as shown in the Addendum). This new table requested by NICE includes the combined solriamfetol and placebo data, and the placebo only data stratified into responders vs non-responders. Jazz was unclear regarding the request and queried the request with NICE who confirmed their request for the data in the format provided in Table 4; Jazz thus complied with the request and submitted the table as requested by NICE. Jazz maintains their

position that placebo-treated patients in the trials would not be considered responders in practice, as in practice patients are not prescribed anything for EDS due to OSA, but instead will receive continuation of their existing standard of care for the underlying OSA. As such, the stratification of placebo into responders and non-responders is inappropriate for modelling. For the same reason, the combination of placebo and solriamfetol data into a pooled data arm is inappropriate and the data cannot be considered representative of clinical practice.

Section 4 ERG analysis of the relationship between change in utility and change in ESS

Jazz understands that the ERG undertook an analysis aimed at mapping ESS change scores to EQ-5D change scores using aggregate data (i.e., the pooled solriamfetol and placebo data requested by the NICE Technical Team). From the details provided, Jazz is unfamiliar with this approach and are unclear that it reflects NICE DSU guidance. Equally, Jazz is unclear on its use in previous technology appraisals or the literature and are unable to verify the appropriateness of the analysis methodology in a decision making context.

Section 5 ERG scenario analysis using response-based utility data

Jazz appreciates the additional work the ERG has done to explore uncertainty, and Jazz agrees that sources of uncertainty should be evaluated. However, Jazz disagrees with the methodological approach that the ERG has employed. Jazz believes that the approach taken by the ERG is unconventional and lacks a level of transparency appropriate for decision making. All four scenarios combine independent utility sources and generate aggregate utility scenarios. This creates ambiguity in the interpretation of uncertainty associated with the independent utility sources within each scenario. Given that utilities are a major driver of the ICER, Jazz would prefer that this uncertainty is presented explicitly in separate scenarios.

Further, Jazz is not clear on the source of the 50/50 split assigned to the two utility sources within the ERG scenarios; the weighting applied has not been robustly explained and Jazz would like to see further information on methodology used to derive this split. In addition, given that uncertainty is conventionally assessed via individual scenarios rather than combined scenarios, Jazz would like to see evidence supporting the methodology used to combine the independent utility sources.

Jazz has a number of concerns regarding the sources of evidence included and excluded in the analysis undertaken by the ERG. These are described in further detail below.

The utilities derived from the NHWS mapping algorithm were initially accepted as the preferred base case by the ERG during the first committee meeting. However, the NHWS analysis is not currently being considered in understanding uncertainty and was given zero weighting by the ERG in their approach. Although the committee noted that the NHWS utility study had limitations in that it was based on cross-sectional data and therefore did not allow for analysis of change scores, Jazz are unaware of any NICE DSU guidance stating that cross-sectional mapping studies are inappropriate where only cross-sectional data are available, as was the case with the NHWS dataset. As confirmed above, the NHWS analysis was completed in line with NICE DSU guidelines thus Jazz is unclear why this dataset has been excluded from the ERG's approach and from the decision making for ID1499.

Further, from a pragmatic review of recent NICE technology appraisals using utility mapping algorithms to derive utility values, Jazz was able to identify two technology appraisals (TA665 and TA565) that used mapping algorithms based on longitudinal data, neither of which appeared to map

change scores (see Appendix 1). Jazz believes the NHWS stands up well against these utility algorithms, being in a relatively large sample size, and completed in line with DSU guidance. The committee further noted that the NHWS study estimates did not seem plausible as quality-of-life estimates were high even at extremely high ESS scores. In contrast, the ERG noted that the impact of treatment on quality of life may have been underestimated, thus making for a conservative scenario. When looking at the utility scores derived using the NHWS algorithm, we see that the range of scores based on ESS scores of 0--24 map to utility scores of [redacted] (see Appendix 2), which are not implausible compared with the utilities produced via the McDaid formula. Jazz believes this highlights the inappropriateness of the trial EQ-5D utilities, which are substantially higher. Given the conflicting perspectives, there is a need for a clear rationale for excluding the NHWS entirely given its alignment to the DSU guidance.

The committee further noted that one of the reasons why the McDaid was preferred was that the ERG had mentioned that the NHWS study may have omitted important predictive variables. Jazz agrees that the use of nonrandomised data can inherently be subject to issues surrounding omission of variables but does not agree that discarding evidence on these grounds is justified given utility data are not required to exclusively be collected in clinical trials in NICE DSU guidance: “Relevant studies can include the clinical trial of the treatment but can also include other studies such as observational studies.” (Rowen et al 2020). Given these points and the absence of a clear rationale, Jazz cannot understand why utilities derived from the NHWS mapping study were excluded from the ERG’s assessment of uncertainty.

Second, although the ERG stated that the utilities derived from the Time Trade Off (TTO) study did not allow for appropriate comparison across technologies being assessed due to the emphasis on sleep in the study, and was therefore not preferred, the study (which followed guidance from the DSU) was conducted to supplement the existing evidence. Therefore, while Jazz accepts that the TTO may not be the most appropriate source of utility values as a base case, Jazz feels that the TTO values should be presented as a scenario to show the impact on the ICERs, if EQ-5D measures are considered likely to underestimate the true impact on quality of life.

Further, the trial EQ-5D showed a lack of responsiveness to change in the primary endpoint (which contradicts the ERG’s view that the NHWS study is a likely an underestimate of utility change). Jazz have provided substantial evidence that the trial EQ-5D data were insufficient to accurately reflect the quality of life improvements in response to solriamfetol. Jazz maintains that the trial EQ-5D are insufficient for decision making and emphasises that all available evidence should be considered in scenario analysis. Specifically, that NHWS is used as the base case, with scenarios analyses investigating the McDaid and TTO utility values.

Appendix 1. Pragmatic review of past technology appraisals where mapping has been performed to derive utility values (note studies where mapping was not identified are not presented)

Table 1 contains summary data for mapping performed to derive utility values in prior NICE TAs.

Table 1. Technology appraisals using mapping algorithms for utility estimates

Appraisal	Mapping data type	N	Change scores mapped
TA381*	Cross sectional	600	Not applicable
TA565	Longitudinal	3,000	No, some participants contributed multiple measures
TA587	Cross sectional	154	Not applicable
TA588	Cross sectional	559	Not applicable
TA590	Cross sectional	152	Not applicable
TA610	Cross sectional†	252	Not applicable
TA613	Cross sectional	607	Not applicable
TA628	Cross sectional	771	Not applicable
TA630	Cross sectional	559	Not applicable
TA631	Cross sectional	8,726	Not applicable
TA640	Cross sectional	154	Not applicable
TA657	Cross sectional	154	Not applicable
TA659	Cross sectional	8,726	Not applicable
TA665	Longitudinal	16,011	No, each participant contributed multiple measures
TA669	Cross sectional	48	Not applicable
TA682	Cross sectional	8,726	Not applicable
TA695	Cross sectional	154	Not applicable
TA698	Cross sectional	771	Not applicable
TA708	Cross sectional	88	Not applicable

* TA381 was superseded by TA620

† Assumed to be cross sectional as data were from a survey

Appendix 2. NHWS mapping parameters and utility estimates

Table 2. NHWS Mapping parameters*

Parameter	Coefficient	Constant
Constant	[redacted]	[redacted]
ESS Score: 0-11	[redacted]	[redacted]
ESS Score: 12-14	[redacted]	[redacted]
SA w/o Narc	[redacted]	[redacted]
SA w Narc	[redacted]	[redacted]
Age	[redacted]	[redacted]
CCIQuan	[redacted]	[redacted]
Female	[redacted]	[redacted]
Married	[redacted]	[redacted]
Medium Income	[redacted]	[redacted]
High Income	[redacted]	[redacted]
BMI	[redacted]	[redacted]
Former Smoker	[redacted]	[redacted]
Current Smoker	[redacted]	[redacted]
Alcohol	[redacted]	[redacted]
Exercise	[redacted]	[redacted]

*UK value set

Table 3. Estimated utility values based on NHWS study

ESS score	Estimated utility*
0	[redacted]
1	[redacted]
2	[redacted]
3	[redacted]
4	[redacted]
5	[redacted]
6	[redacted]
7	[redacted]
8	[redacted]
9	[redacted]
10	[redacted]
11	[redacted]
12	[redacted]
13	[redacted]
14	[redacted]
15	[redacted]
16	[redacted]
17	[redacted]
18	[redacted]
19	[redacted]
20	[redacted]
21	[redacted]
22	[redacted]
23	[redacted]
24	[redacted]

* Estimated utility values as calculated using the UK value set NHWS presented in Table 2

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

Solriamfetol for treating excessive waketime sleepiness caused by obstructive sleep apnoea

Evidence Review Group critique of the company's additional EQ-5D analysis (12 November 2021)

Produced by	Southampton Health Technology Assessments Centre (SHTAC)
Authors	Joanne Lord
Date completed	6 December 2021

Commercial in confidence (CIC) information in blue

Academic in confidence (AIC) information in yellow

1. Introduction

Following a request from NICE, Jazz Pharmaceuticals submitted additional evidence and analysis relating to EQ-5D data from the TONES 3 trial (document dated 12/11/21). This addendum includes ERG critique of the company's analysis around the 'ceiling effect' (section 2 below), summary and comments on the additional EQ-5D data provided by the company (section 3) and ERG cost-effectiveness scenarios based on the additional EQ-5D data (sections 4).

2. ERG Critique of company analysis of EQ-5D ceiling effect

The company states that the baseline utility values from TONES 3 "are inconsistent with the utility profile that would be expected in this patient population". They report mean baseline EQ-5D scores for the TONES 3 revised base case population (baseline ESS>12) as [redacted] and [redacted] respectively for responders and non-responders (Table 4 in the company's additional evidence report). For comparison, EQ-5D population norms for people of a similar age (50-55 years) in the general population are 0.9345 (95% CI: 0.927 to 0.941) for people reporting no history of a health condition and 0.8344 (0.824 to 0.843) for people reporting history of a health condition (Ara and Brazier 2011 supplement table A4).[1]

The company highlight the observed 'ceiling effect', in which a proportion of TONES 3 respondents indicated no problems on any of the EQ-5D dimensions at baseline, hence scoring a perfect utility of 1 and leaving no room for improvement (see discussion in section B.3.4 of the company submission). This is a well-known phenomenon that has been observed in many studies, including the two cited by the company.[2] [3] We note that although these two cited papers warned about the potential impact of high utility scores from the EQ-5D-5L on responsiveness, they both reached favourable conclusions about the psychometric properties of the EQ-5D-5L and neither suggested statistical manipulation such as discarding or selectively sampling data to avoid or reduce the problem.

The company state that they did consider a simple truncation of the dataset, excluding patients with a baseline utility above a certain value, but concluded that this would have biased the analysis and that "it is reasonable to expect *some* patients will report a baseline utility of 1 in almost every dataset assessing EQ-5D". We agree. Instead, the company used selective re-sampling of data from the TONES 3 dataset to simulate results with mean baseline utilities closer to reported estimates from previous literature (Table 3 in the company's report of 12/11/21).

An obvious problem with this as a method of exploring the impact of an EQ-5D ceiling effect, is that the studies from the literature that the company compare against (Jenkinson 1997/1998, Chakravorty 2002, Mar 2003 and McMillan 2014)[4-8] also used the EQ-5D, and so should have been equally susceptible to such a ceiling effect as the TONES 3 study. In fact, given the age of the target studies, they would have used the EQ-5D-3L, which is equally or more vulnerable to ceiling effects than the EQ-5D-5L.[3] However, there is another potential rationale for the company's approach. It is essentially a form of calibration, which can be an appropriate modelling technique in some circumstances: for example to estimate unobserved outcomes or to adjust results to be more representative of a population of interest. There is therefore a key question of whether the studies used as targets for the company's calibration are more representative of the relevant population than TONES 3.

The company does not discuss this or their reasons for using the four target sources for the calibration (Jenkinson 1997/1998, Chakravorty 2002, Mar 2003 and McMillan 2014).[4-8] We note that these studies are four of the five studies identified from the company's systematic review of health-related quality of life that reported EQ-5D utility scores (see Table 27 in the ERG report for a summary). We question whether the company have used the correct baseline EQ-5D values from these studies. For three studies (Jenkinson 1997/1998, Chakravorty 2002 and Mar 2003),[4-7] the company use baseline scores prior to the introduction of CPAP (0.79, 0.73 and 0.74 respectively), which does not align with members of the current appraisal population who were on primary OSA therapy at baseline. Mean EQ-5D scores in the Jenkinson, Chakravorty and Mar studies were higher after the introduction of CPAP (0.84, 0.77 and 0.81 respectively). The mean utility for the lifestyle advice arm in the Chakravorty trial was 0.77 (at baseline and at end of trial). The 'utilities' used in the company's analysis from the McMillan study (0.666 and 0.668) are actually QALYs, not utilities. We agree with the company's omission of the fifth study reported in ERG Table 27, the TOMADO trial (Quinnell et al. 2014).[9] This was a trial of mandibular devices for a population with mild to moderate OSA, not using CPAP at baseline.

The ERG concludes that the company's utility estimates from their 'ceiling effect' analysis in Table 3 of their report dated 12/11/21 are poorly justified, highly uncertain and likely to be biased. It is not clear why baseline EQ-5D values from the selected reference trials would be any more accurate at assessing utility for the population of interest than EQ-5D in the TONES 3 trial. The company does not justify the choice of trials, the use of baseline utilities prior to introduction of CPAP, or make the case that the populations in the reference trials are more representative of the current target population than that in the TONES 3 trial.

3. Commentary on additional EQ-5D information provided by the company

The company report mean EQ-5D utility at baseline and week 12 by treatment arm and responder status for the subgroup of people with ESS>12 at baseline from the TONES3 trial in Table 4 of their submitted document.

The ERG has several concerns over the validity of the reported utility estimates:

- The baseline EQ-5D value for solriamfetol responders in the company's additional evidence report is [redacted] in Table 1 and [redacted] in Table 4. It appears that the latter value is correct as it is consistent with the week 12 and change from baseline values reported in company Table 4.
- It is not stated if the reported EQ-5D-5L index values (utilities) are calculated using the NICE preferred method, with the van Hout crosswalk procedure using the UK EQ-5D-3L value set. A footnote to Table 14.2.10.1 in the clinical study report for TONES 3 states: "[redacted]
- It is not specified that trial participants randomised to the unlicensed 300 mg dose of solriamfetol have been excluded. We cannot verify this as the sample sizes for the mean utility values are not reported.
- Sample sizes and measures of variance around the mean values are not reported.
- It is stated in the footnote to company Table 4 that the data reflect unadjusted raw individual patient-level data from TONES 3. This implies that results are simple means within the relevant groups and that the mean change in EQ-5D is a simple difference of means. If so, this differs from the method of analysis for quality of life outcomes in the trial, which used a mixed-effect repeated measures (MMRM) model with fixed effects for treatment and dose, visit, treatment-by-visit interaction, baseline value of the efficacy endpoint, and randomization stratification factor (primary OSA therapy at baseline).[10]
- The footnote to company Table 4 also states that patients without any post baseline EQ-5D scores were excluded from the analysis, and that last observation carried forward (LOCF) was used to impute other missing values. The company has not reported the quantity of missing data or the pattern of missingness. We are concerned that the LOCF method may have biased the results given the different patterns of change in EQ-5D index scores during 12-week follow up for the TONES 3 trial arms (see Figure 5 in the company's clarification responses for the modified intention to treat population).

4. ERG analysis of the relationship between change in utility and change in ESS

We investigated the relationship between change in utility and change in ESS using the mean utility results reported in the company's Table 4 and TONES 3 individual patient data (IPD) that is included in the company's model. For this analysis we used the revised 'regression to the mean' (RTM) version of the company model dated 9/8/21, which includes baseline and unadjusted ('uncentred') 12-week ESS data for patients from the placebo arm and the 37.5 mg, 75 mg and 150 mg solriamfetol arms of the TONES 3 trial. Table 1 below shows the sample sizes by treatment and response status from this IPD dataset, restricted to the subgroup (baseline ESS>12) and using the response definition (ESS reduction ≥ 2 points over 12 weeks) as specified in the ACD. Given these numbers of responders and non-responders in the placebo and solriamfetol arms, we obtained the same mean utility results for the pooled (solriamfetol and placebo arms) as reported in company Table 4.

ERG estimates of mean ESS at baseline, 12 weeks and change from baseline obtained from the model IPD are shown in Table 1 below. Combining these results with the company's reported utility results for the pooled treatment arms, we estimate that a one point reduction in mean ESS is associated with an increase in mean utility of [redacted] (on the scale from 0 for a health state considered equivalent to death to 1 for 'perfect health').

We emphasise that this estimate is highly uncertain. In addition to our concerns about the company's reporting of the utility estimates in Table 4 (as listed in section 3 above), we note that the utility estimates are only reported to three decimal places and that we are combining these with ESS estimates from the unadjusted IPD dataset from the model. Results are similar for responders and non-responders in the pooled population: [redacted] and [redacted] respectively (we only report results to three decimal places in Table 1 to reflect rounding of mean utility change in the company's table). It is difficult to interpret differences in the estimated utility/ESS relationship between treatment arms and between responders and non-responders in the absence of an appropriate statistical analysis.

Table 1. TONES 3 EQ-5D and ESS results by response status and treatment arm patients with baseline ESS >12

Treatment [c]	Response [a]	N (%) [c]	Mean utility (EQ-5D) [b]			Mean ESS [c]			Mean change in utility per unit change in ESS [c]
			Baseline	Week 12	Change	Baseline	Week 12	Change	
Solriamfetol (n=166)	Responder	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Non-responder	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Placebo (n=94)	Responder	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Non-responder	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pooled (n=260)	Responder	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Non-responder	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Source: Produced by the ERG using utility data from Table 4 of the company's additional evidence report 12/11/21 and raw individual patient data (IPD) reported in the company's economic model (regression to the mean version dated 09/08/21)

[a] Response defined as ESS reduction of ≥2 points from baseline to week 12 per the committee's preferred assumption

[b] Mean utilities from company additional analysis Table 4 (12/11/21)

[c] Sample sizes, % response, ESS and mean change in utility per unit change in ESS estimated by ERG

5. ERG scenario analysis using response-based utility data

In response to a request from NICE, we conducted additional scenario analyses using the new response-based utility estimates for the pooled treatment arms. We started with the ERG's adapted version of the company's three models (dated 09/08/21) that we had used to produce our addendum of 17/09/21: including the company's preferred 'Hawthorne' model (with centred week 12 ESS data), their versions of 'regression to the mean' (RTM) and 'true placebo' models, and a spreadsheet used to produce weighted mean results for a mixture of the three models. Our adapted versions of these models had included an option to use utility estimates based on a mixture of the McDaid ESS to utility mapping and previously reported EQ-5D results from the TONES 3 trial (mean change in utility by treatment arm).[11]

For the new analyses, we edited the 'efficacy' and 'results' sheets of each of the three models (Hawthorne, RTM and True placebo) to add options to combine utility estimates from the McDaid formula with estimates from the TONES 3 pooled response-based EQ-5D results discussed above. We included two options for estimation of the TONES 3 pooled response-based utilities:

- **Method 1** – baseline utility for both treatment arms [redacted], adjusted for responders and non-responders by adding the company's reported mean changes in EQ-5D from baseline to week 12 ([redacted] and [redacted] respectively). This gives utility estimates of [redacted] for responders and [redacted] for non-responders, irrespective of treatment arm (see Table 2 below).
- **Method 2** – McDaid ESS to EQ-5D mapping formula, with the slope coefficient replaced with the ERG's estimate of the mean change in EQ-5D utility per unit change in ESS. The coefficient from the analysis by McDaid and colleagues was -0.0096984 and the ERG estimate from TONES 3 [redacted] (Table 1 above).[11] Results are shown in Table 2 below. Unlike method 1, the utility estimates from method 2 differ by treatment arm and dose.

For comparison, Table 2 also shows utility estimates from the original McDaid formula. This gives bigger differences in mean utilities between responders and non-responders and between solriamfetol and standard care arms than the TONES 3 based estimates. Method 2 gives bigger responder versus non-responder and solriamfetol versus standard care differences than method 1, because the former takes account of between-arm differences in mean ESS within the responder and non-responder groups.

Table 2 ERG utility estimates from McDaid formula and TONES 3

Treatment and dose	% response	Responders (R)		Non-responders (NR)		Utility (R vs. NR)	Overall	
		Mean Δ ESS	Mean utility	Mean Δ ESS	Mean utility		Mean utility	Increment versus SC
Method 1 TONES 3 pooled response-based EQ-5D (mean utility change)								
Standard care (SC)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
Solriamfetol 37.5 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Solriamfetol 75 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Solriamfetol 150 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Solriamfetol weighted [a]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Method 2 TONES 3 pooled response-based EQ-5D (McDaid formula with slope coefficient from ERG analysis [redacted])								
Standard care	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Solriamfetol 37.5 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Solriamfetol 75 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Solriamfetol 150 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Solriamfetol weighted [a]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
McDaid ESS to EQ-5D mapping formula (slope coefficient -0.0096984)[11]								
Standard care	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Solriamfetol 37.5 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Solriamfetol 75 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Solriamfetol 150 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Solriamfetol weighted [a]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Source: ERG estimates based on IPD ESS (uncentred) and EQ-5D by response for pooled treatment arms (company report 12/11/21)

[a] Weighted by assumed dose mix: [redacted] 37.5 mg; [redacted] 37.5 mg; [redacted] 150 mg

Abbreviations: R responder; NR non-responder; Δ ESS change in Epworth Sleepiness Scale; SC standard care

Note that the ERG calculations in Table 2 (as in Table 1) use unadjusted (non-centred) IPD. The company's Hawthorne, RTM and True placebo versions of the model include assumptions over the causal mechanism of the placebo effects and whether these would be observed in routine clinical practice, which over-ride some of the ESS and utility results as reported in Table 2. In the Hawthorne model, the mean change in ESS observed in the standard care arm is subtracted from final ESS results from all arms (centred data). Thus the mean changes in ESS used in this version of the model are lower than those reported in Table 2. In the true placebo version of the model, the mean change in ESS in the standard care arm is assumed to be zero, while ESS in the solriamfetol arms is not adjusted. The company use unadjusted ESS data in their RTM model, but do not differentiate results for 'responders' and 'non-responders' in the standard care arm. Instead they use the mean ESS reduction across this whole standard care arm: [redacted], for which the McDaid utility estimate is [redacted]. Furthermore, they apply this same utility to non-responders in the solriamfetol arms from year 2 onwards, which has the effect of increasing overall utility estimates for solriamfetol above the values reported in Table 2.

Table 3 below shows the results for additional ERG scenario analyses. These analyses start with the company's revised base case from their ACD response (dated 25/06/2021). We added costs for hospitalisation estimated from TONES 5 treatment related serious adverse events (TRSAE) for solriamfetol arms (no adverse event costs in the placebo arm). This provided the basis on which the other scenario analyses were conducted.

We conducted four scenario analyses based on combinations of:

- An equal mix of utility estimates from the McDaid formula and ERG estimates from the pooled response-based TONES 3 EQ-5D results, calculated using either method 1 or method 2 described above.
- The company's preferred Hawthorne model or an equal mix of cost and QALY results from the Hawthorne, 'True placebo' and 'Regression to the mean' (RTM) models.

Table 3 ERG scenarios: deterministic with PAS for solriamfetol

Placebo mechanism		Treatment	Total		Incremental		ICER
			Costs	QALYs	Costs	QALYs	£ / QALY
Company's base case		SC alone	£4,810	11.524			
		SC + Sol	[redacted]	11.969	[redacted]	0.445	[redacted]
+ TONES 5 TRSAE hospital costs		SC alone	£0	11.524			
		SC + Sol	[redacted]	11.969	[redacted]	0.445	[redacted]
Utilities 50% McDaid formula and 50% from trial calculated using method 1 (mean utility gain [redacted] for responders and [redacted] for non-responders, all treatments)							
4c	Hawthorne model	SC alone	£0	14.430			
		SC + Sol	[redacted]	14.697	[redacted]	0.266	[redacted]
7c	Equal mix of 3 models	SC alone	£0	14.591			
		SC + Sol	[redacted]	14.867	[redacted]	0.277	[redacted]
Utilities 50% McDaid formula and 50% from trial calculated using method 2 (mean utility gain per unit reduction in ESS [redacted] from trial)							
4c	Hawthorne model	SC alone	£0	14.956			
		SC + Sol	[redacted]	15.206	[redacted]	0.251	[redacted]
7c	Equal mix of 3 models	SC alone	£0	15.095			
		SC + Sol	[redacted]	15.398	[redacted]	0.303	[redacted]

Source: ERG adapted version of the company's submitted models dated 09/08/21
Abbreviations: SC standard care; Sol solriamfetol; TRSAE treatment-related serious adverse events; PAS patient access scheme

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Solriamfetol for treating excessive waketime sleepiness caused by obstructive sleep apnoea

Evidence Review Group critique of the company's additional EQ-5D analysis (12 November 2021)

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Date completed	13 December 2021

Commercial in confidence (CIC) information in blue

Academic in confidence (AIC) information in yellow

1. Introduction

In response to a request from NICE, we have conducted the analyses in our addendum of 6 December 2021 for subgroups of patients from the TONES 3 trial who were and were not using primary OSA therapy at baseline. Primary OSA therapy consisted mostly of CPAP, but included other devices or surgery for a minority of patients.

2. Estimated relationship between ESS and EQ-5D by subgroup

In our previous addendum, we estimated a mean EQ-5D utility increase of [redacted] per unit reduction in ESS over 12 weeks of follow up: similar for 'responders' and 'non-responders' (estimates from pooled treatment arms for people with baseline ESS>12, see section 4 ERG addendum 6/12/21). Table 1 below shows ERG estimates of this coefficient for subgroups using/not using primary OSA therapy at baseline in the TONES 3 trial. We caution that these results are subject to additional uncertainties. First, we only have utility results for the overall population, which we use for both subgroups, which might not be accurate. Second, the sample size for the subgroup not using primary OSA therapy at baseline was small, with very few non-responders. In the subgroup using primary OSA therapy at baseline, the estimated coefficients for both responders and non-responders were similar to that in the overall population (pooled treatment arms, ESS>12). This coefficient was also similar for responders who were not using primary OSA therapy at baseline. Results are not estimable for non-responders who were not using primary OSA therapy at baseline.

3. Utility estimates by subgroup

Table 2 and Table 3, respectively, show utility estimates for people using and not using primary OSA therapy at baseline. Using 'method 1', fixed utilities for responders ([redacted]) and non-responders ([redacted]) regardless of treatment, the estimated utility gain with solriamfetol (weighted by assumed dose usage) compared with placebo is slightly higher for the subgroup not using primary OSA therapy at baseline ([redacted]) than for the subgroup who were ([redacted]). This result is due to small differences between the subgroups in the estimated proportions of responders by treatment arm. Also note that response and hence utility differ between the solriamfetol dose arms. So the estimates of overall utility gain are affected by the assumed dose split.

Similarly, using the McDaid formula to estimate utilities, results are more favourable for the subgroup not using primary OSA therapy at baseline than for those who were. Using the published McDaid formula (slope coefficient -0.0097), estimated utility gain for solriamfetol

versus placebo is [redacted] for people using primary OSA therapy at baseline and [redacted] for people who were not. Applying the slope coefficient of [redacted] estimated from the TONES 3 data ('method 2'), utility gain is [redacted] for people using primary OSA therapy at baseline and [redacted] for people who were not.

4. Cost-effectiveness results by subgroup

Finally, we show the impact of the two alternative methods of utility estimation when applied in the company's models. We report two utility scenarios as requested by NICE:

- 50% from the McDaid formula and 50% estimated from trial data using method 1 (fixed utility of [redacted] for responders and [redacted] for non-responders).
- 50% from the McDaid formula and 50% using an adjusted version of the McDaid formula with a slope coefficient of [redacted] estimated from TONES 3 data.

The ERG applied these utility estimates to the company's three models (Hawthorne, regression to the mean (RTM), and true placebo), which differ in their assumptions about the cause of the placebo response. The two methods of utility estimation have different effects in the three models, in particular results from the RTM model are more favourable under utility method 2 than method 1. This is due to the company's assumption that non-responders to solriamfetol revert to the same mean ESS as observed in the whole placebo arm from year 2 onwards, which gives a better utility with the McDaid formula than with method 1 where we continue to apply the fixed non-responder utility.

Table 4 below reports ERG cost-effectiveness estimates, starting with the company's revised base case and adding hospitalisation costs estimated from treatment related serious adverse events in the TONES 5 open label study. These two scenarios use the company's preferred NHWS utility mapping and the Hawthorne version of the model. Adding the mixed utility results (50% McDaid and 50% trial-based estimates with either method 1 or 2) increases the ICERs across all three models. In each scenario, ICERs are rather less favourable for the subgroup who were using primary OSA therapy at baseline and more favourable for the subgroup who were not.

Table 1. TONES 3 EQ-5D and ESS by baseline use of primary OSA therapy, response status and treatment arm

Treatment [c]	Response [a]	N (%) [c]	Mean utility (EQ-5D) [b]			Mean ESS [c]			Mean change in utility per unit change in ESS [c]
			Baseline	Week 12	Change	Baseline	Week 12	Change	
TONES 3 population with baseline ESS>12									
Solriamfetol (n=166)	Responder Non-responder								
Placebo (n=94)	Responder Non-responder								
Pooled (n=260)	Responder Non-responder								
Subgroup with ESS>12 and using primary OSA therapy at baseline									
Solriamfetol (n=[redacted])	Responder Non-responder								
Placebo (n=[redacted])	Responder Non-responder								
Pooled (n=[redacted])	Responder Non-responder								
Subgroup with ESS>12 and not using primary OSA therapy at baseline									
Solriamfetol (n=[redacted])	Responder Non-responder								
Placebo (n=[redacted])	Responder Non-responder								
Pooled (n=[redacted])	Responder Non-responder								

Source: Produced by the ERG using utility data from Table 4 of the company's additional evidence report 12/11/21 and raw individual patient data (IPD) reported in the company's economic model (regression to the mean version dated 09/08/21)

[a] Response defined as ESS reduction of ≥2 points from baseline to week 12 per the committee's preferred assumption

[b] Mean utilities from company additional analysis Table 4 (12/11/21)

[c] Sample sizes, % response, ESS and mean change in utility per unit change in ESS estimated by ERG

NE not estimable

Table 2 ERG utility estimates: subgroup with ESS>12 and using primary OSA therapy at baseline

Treatment and dose	% response	Responders (R)		Non-responders (NR)		Utility (R vs. NR)	Overall	
		Mean Δ ESS	Mean utility	Mean Δ ESS	Mean utility		Mean utility	Increment versus SC
Method 1 TONES 3 pooled response-based EQ-5D (baseline [redacted], utility change [redacted] for responders, [redacted] for non-responders)								
Standard care (SC)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
Solriamfetol 37.5 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Solriamfetol 75 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Solriamfetol 150 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Solriamfetol weighted [a]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Method 2 McDaid formula with TONES 3 subgroup baseline mean ESS ([redacted]) and slope coefficient [redacted])								
Standard care	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
Solriamfetol 37.5 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Solriamfetol 75 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Solriamfetol 150 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Solriamfetol weighted [a]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
McDaid formula with TONES 3 baseline mean ESS ([redacted]) and McDaid slope coefficient (-0.0097)								
Standard care	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
Solriamfetol 37.5 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Solriamfetol 75 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Solriamfetol 150 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Solriamfetol weighted [a]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Source: ERG estimates based on IPD ESS (uncentred) and EQ-5D by response for pooled treatment arms (company report 12/11/21)

[a] Weighted by assumed dose mix: [redacted] 37.5 mg; [redacted] 37.5 mg; [redacted] 150 mg

Abbreviations: R responder; NR non-responder; Δ ESS change in Epworth Sleepiness Scale; SC standard care

Table 3 ERG utility estimates: subgroup with ESS>12 and not using primary OSA therapy at baseline

Treatment and dose	% response	Responders (R)		Non-responders (NR)		Utility (R vs. NR)	Overall	
		Mean Δ ESS	Mean utility	Mean Δ ESS	Mean utility		Mean utility	Increment versus SC
Method 1 TONES 3 pooled response-based EQ-5D (baseline [redacted], utility change [redacted] for responders, [redacted] for non-responders)								
Standard care (SC)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
Solriamfetol 37.5 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Solriamfetol 75 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Solriamfetol 150 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Solriamfetol weighted [a]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Method 2 McDaid formula with TONES 3 subgroup baseline mean ESS ([redacted]) and slope coefficient [redacted])								
Standard care	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
Solriamfetol 37.5 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Solriamfetol 75 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Solriamfetol 150 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Solriamfetol weighted [a]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
McDaid formula with TONES 3 baseline mean ESS ([redacted]) and McDaid slope coefficient (-0.0097)								
Standard care	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
Solriamfetol 37.5 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Solriamfetol 75 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Solriamfetol 150 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Solriamfetol weighted [a]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Source: ERG estimates based on IPD ESS (uncentred) and EQ-5D by response for pooled treatment arms (company report 12/11/21)

[a] Weighted by assumed dose mix: [redacted] 37.5 mg; [redacted] 37.5 mg; [redacted] 150 mg

Abbreviations: R responder; NR non-responder; Δ ESS change in Epworth Sleepiness Scale; SC standard care

Table 4 ERG scenarios by use of primary OSA therapy at baseline: deterministic with PAS for solriamfetol

Placebo mechanism		Treatment	TONES 3 population (n=260) Total Costs	Total QALYs	ICER £ / QALY	Using primary OSA therapy at baseline (n=[redacted]) Total Costs	Total QALYs	ICER £ / QALY	Not using primary OSA therapy at baseline (n=[redacted]) Total Costs	Total QALYs	ICER £ / QALY
Company's base case		SC alone	£4,810	11.524		£4,811	11.575		£4,810	11.373	
		SC + Sol	[redacted]	11.969	[redacted]	[redacted]	11.991	[redacted]	[redacted]	11.893	[redacted]
+ TONES 5 TRSAE hospital costs		SC alone	£0	11.524		£0	11.575		£0	11.373	
		SC + Sol	[redacted]	11.969	[redacted]	[redacted]	11.991	[redacted]	[redacted]	11.893	[redacted]
Utilities 50% McDaid formula and 50% from trial calculated using method 1 (mean utility gain [redacted] for responders and [redacted] for non-responders, all treatments and subgroups)											
4c	Hawthorne model	SC alone	£0	14.430		£0	14.444		£0	14.392	
		SC + Sol	[redacted]	14.697	[redacted]	[redacted]	14.691	[redacted]	[redacted]	14.699	[redacted]
7c	Equal mix of 3 models	SC alone	£0	14.591		£0	14.597		£0	14.572	
		SC + Sol	[redacted]	14.867	[redacted]	[redacted]	14.858	[redacted]	[redacted]	14.883	[redacted]
Utilities 50% McDaid formula and 50% from trial calculated using method 2 (mean utility gain per unit reduction in ESS [redacted] from trial, all treatments and subgroups)											
4c	Hawthorne model	SC alone	£0	14.956		£0	14.969		£0	14.917	
		SC + Sol	[redacted]	15.206	[redacted]	[redacted]	15.197	[redacted]	[redacted]	15.218	[redacted]
7c	Equal mix of 3 models	SC alone	£0	15.095		£0	15.099		£0	15.082	
		SC + Sol	[redacted]	15.398	[redacted]	[redacted]	15.384	[redacted]	[redacted]	15.427	[redacted]

Source: ERG adapted version of the company's submitted models dated 09/08/21

Abbreviations: SC standard care; Sol solriamfetol; TRSAE treatment-related serious adverse events; PAS patient access scheme; mITT modified intention to treat population; OSA obstructive sleep apnoea