NICE National Institute for Health and Care Excellence

Public observer slides – no confidential information

Pitolisant hydrochloride for treating excessive daytime sleepiness caused by obstructive sleep apnoea [ID1065]

Lead team presentation

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Company: Lincoln Medical

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Excessive waketime sleepiness (Obstructive sleep apnoea)

Overview of the condition

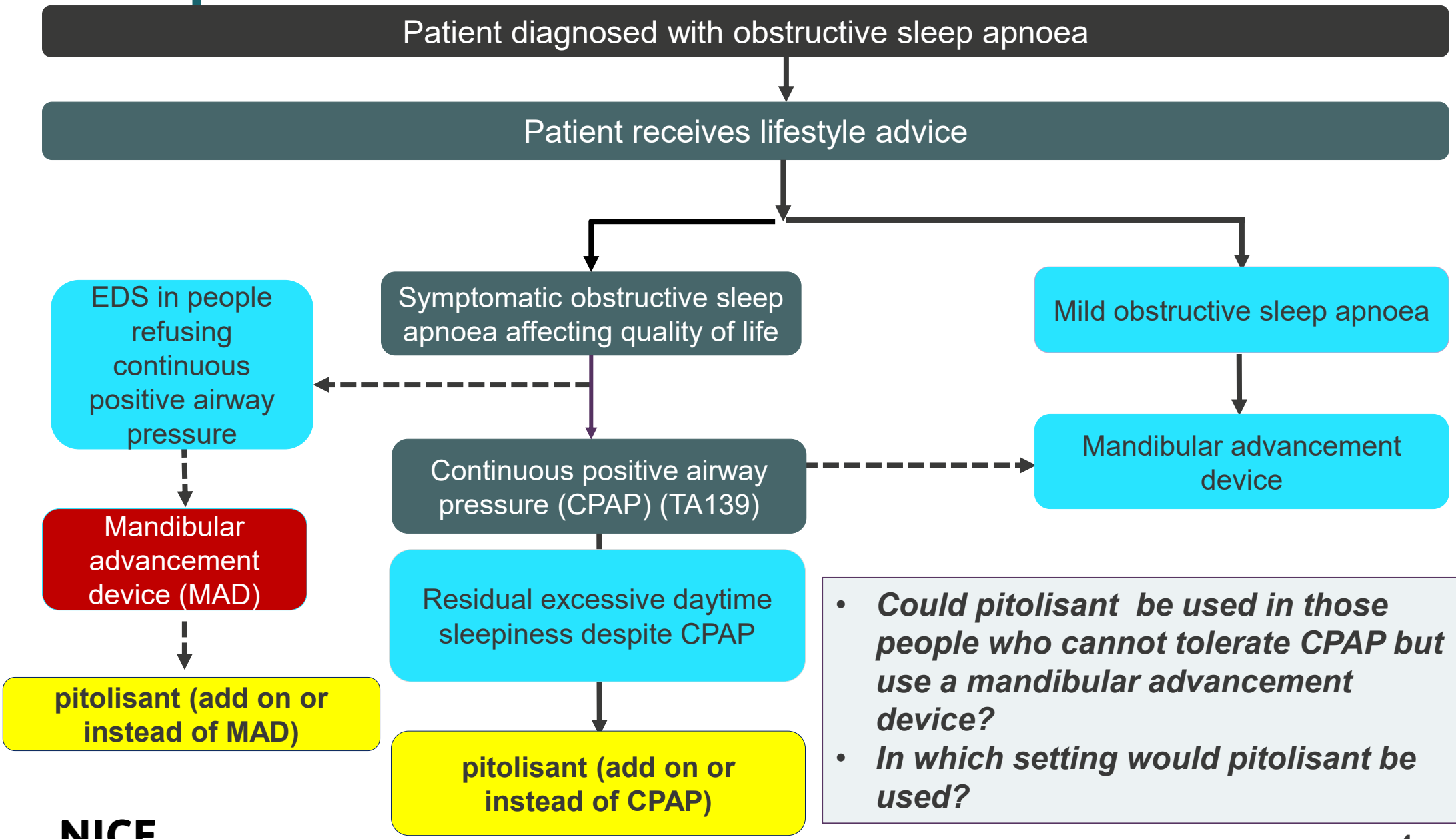
- Excessive waketime sleepiness (hypersomnia) means people struggle to stay awake and alert during the day (or equivalent waking hours).
  - leads to an irrepressible need to sleep or unintended lapses into drowsiness or sleep.
- One cause of excessive daytime sleepiness (EDS) is obstructive sleep apnoea (OSA).
  - OSA is a chronic, common sleep disorder, characterised by the repeated occurrence of complete (apnoea) or partial (hypopnoea) closures of the upper airway during sleep.
  - Approx.1.5 million adults in the UK have OSA (2.32% of the overall population); around 22% of these are diagnosed and treated.
  - Affects daily life, including education, employment, driving, relationships and emotional health and general health.
  - OSA negatively impacts sleep quality and may result in napping, decreased energy, irritability, feeling unrefreshed or having headaches upon awakening, reduced enjoyment of usual activities, and impaired work performance.

Abbreviations: EDS; Excessive daytime sleepiness OSA; Obstructive sleep apnoea

Pitolisant (Ozawave, Lincoln medical)

Mechanism of action	Pitolisant is an orally active histamine H3-receptor antagonist/inverse agonist which, via its blockade of histamine auto-receptors, enhances the activity of brain histaminergic neurones. It also modulates various neurotransmitter systems, increasing acetylcholine, noradrenaline, and dopamine release in the brain.
Marketing authorisation	xxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxx xxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxx xxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxx xxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxx
Dosage and Administration	Pitolisant should be used at the lowest effective dose, depending on an individual's response and tolerance, according to an up-titration scheme, without exceeding the dose of 18 mg/day: Initial dose of 4.5 mg (one 4.5 mg tablet) per day can be increased to 9 mg (two 4.5 mg tablets) per day in week 2. The dose can be titrated up or down from week 3 (to one 18 mg tablet) or down to 4.5 mg per day.
Price	xxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxx xxxxxxxxxxxxxxxxxxxxxxx

Treatment Pathway – Current and proposed with pitolisant



- ***Could pitolisant be used in those people who cannot tolerate CPAP but use a mandibular advancement device?***
- ***In which setting would pitolisant be used?***

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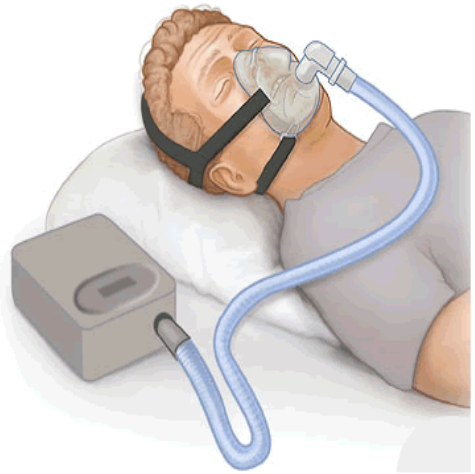
Patient and carer perspectives

The Sleep Apnoea Trust Association (SATA)



Overview

- Can be very debilitating and take a toll on patients and family members.
- Poor understanding of the condition amongst some primary care professionals.
- Diagnosis and referral can be delayed, sleep clinic referral is not necessarily the first consideration for a GP when presented with a OSA symptoms.
- Patient access to OSA diagnosis and treatment is inconsistent.

Current experience of treatment

- SATA members were very satisfied with their treatment for OSA from sleep clinics.
- Many patients describe their CPAP as life-changing
- CPAP treatment is associated with difficulties
  - There is discomfort and restriction of having to sleep connected to the machine, also its cleaning and maintenance
  - Use while flying can be an issue as well as the use of the machine in hotels (plug access etc)
- In terms of unmet need no drug therapy exists for OSA
- Partners should be considered to have the same importance as carers

Clinician perspective

Overview

- Significant proportion of patients remain with excessive daytime sleepiness (EDS) despite maximal NHS available therapy (in the most cases CPAP therapy) despite being compliant.
- Little or no other options for this group of patients currently.

Unmet need

- OSA not treated pharmacologically (modafinil in rare cases).
- OSA services in the UK are over stretched with diagnosis and treatment of OSA with CPAP (especially post-COVID-19).
- Agree that would offer medication if available for those cases were symptoms persist despite lifestyle changes and CPAP use.

Current Treatment

- No clear treatment pathway in the UK, large variation exists based on exposure of cases e.g. larger centres with access to advanced testing who treat patients with sleep conditions like Narcolepsy may treat patient differently to other centres.
- The pathway would need a total change as patients with EDS would need to be followed up and also those already on CPAP would also need to be captured.
- Pitolisant would only be prescribed in severe cases that still present excessive day time sleepiness after CPAP. Mild cases that are being managed with a MAD would not receive pitolisant as an add-on.
- It is worth noting that anxiety and depression can affect the level of awakeness the next day. Therefore, clinicians would need to assess other medical problems, medication, depression and sleep hygiene habits before considering adding pitolisant.

Evidence from HAROSA I

Prospective, multicentre, randomised, double-blind, placebo-controlled trial followed by open-label extension.

Population

- Adults who received CPAP therapy at least 3 months but still reported EDS
- Baseline ESS score ≥12
- BMI ≤ 40 kg/m²

Key exclusions:

- Co-existing narcolepsy
- Psychiatric illness
- CV system abnormalities
- Severe co-morbidities

Intervention
12-week double-blind
Patients= 244

Pitolisant at 5mg, 10 mg or 20 mg per day.

Patients=183

Placebo (oral tablet)

Patients=61

Open-label period
40-week
Patients=199

Pitolisant at 5mg, 10 mg or 20 mg per day.

Patients from pitolisant group = 151

Patients from placebo group =48

Primary Endpoint: (Used in economic model) ESS between baseline and end of study treatment.

12 week results - HAROSA I (previous CPAP group)

Baseline characteristics

- Patients enrolled= 244

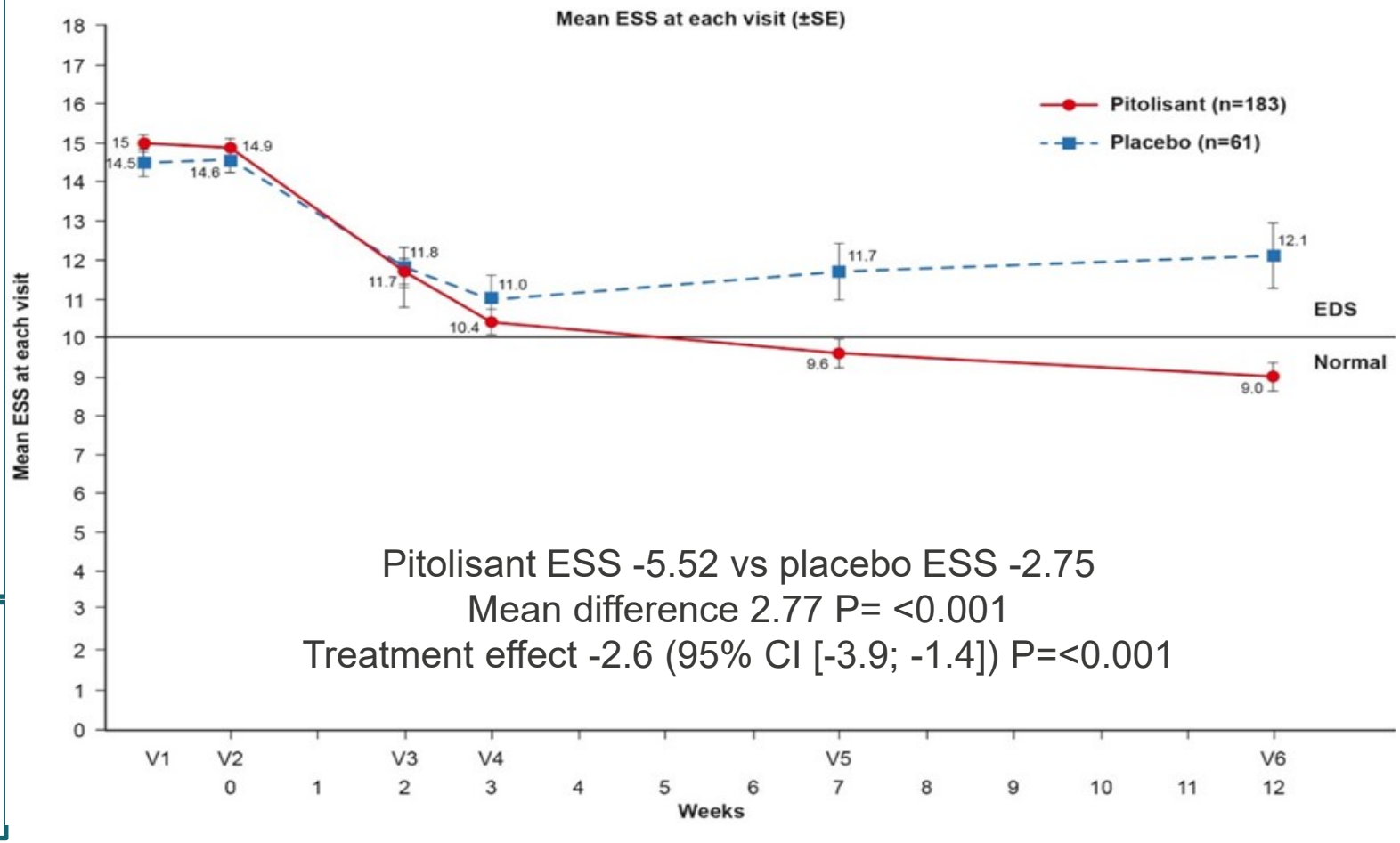
(183 pitolisant/ 61 placebo)

- Age (years) 53.8
- Male 81.4%
- BMI 32.66
- Professionally active 63.9%
- Working days per week 5.1
- CV history 60.7%
- ESS 14.9
- Pichot Fatigue scale 13.2

Statistical analysis

ANCOVA methodology and all tests were performed two sided at 5% level of significance.

ESS mean score at each visit (±SE) in the **12-week double-blind period**



Pitolisant ESS -5.52 vs placebo ESS -2.75
Mean difference 2.77 P= <0.001
Treatment effect -2.6 (95% CI [-3.9; -1.4]) P=<0.001

Pitolisant reduced daytime sleepiness with an ESS decrease of -5.52 in patients receiving CPAP.

- ***Is an average reduction of ESS score of -2.7 clinically significant?***

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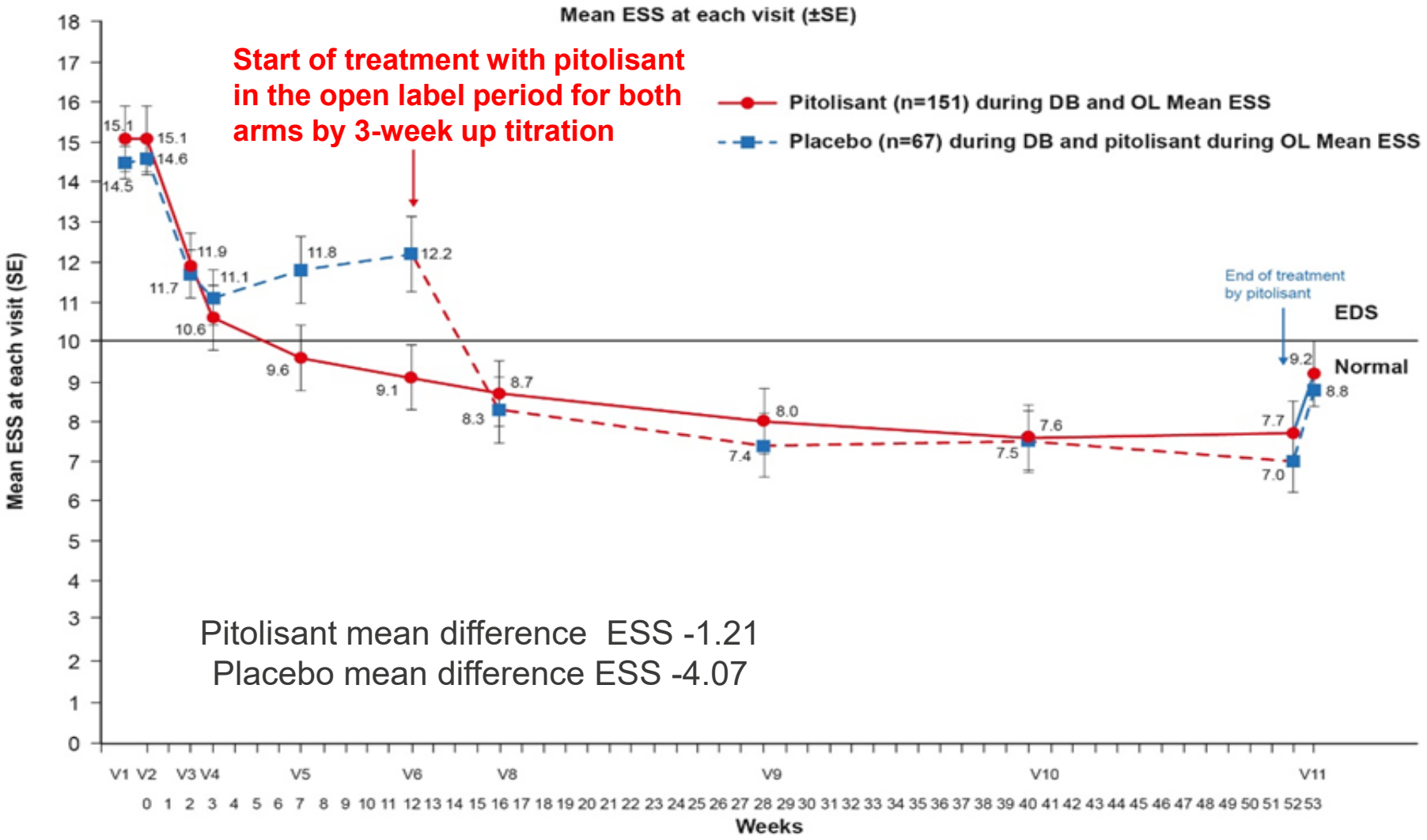
Overall results – HAROSA I (previous CPAP group)

ESS mean score (±SE) during the **overall study period**



Pitolisant mean difference ESS -1.21
Placebo mean difference ESS -4.07

By the end of the 52-week study period, patients who had received CPAP and pitolisant for the duration of the study had ESS scores of 8.1.

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Evidence from HAROSA II

Prospective, multicentre, randomised, double-blind, placebo-controlled trial followed by open-label extension.

Population

- Adult patients who **refused** CPAP and still complain of EDS
- Baseline ESS score ≥12
- BMI ≤ 40 kg/m²

Key exclusions:

- Co-existing narcolepsy
- Psychiatric illness
- CV system abnormalities
- Severe co-morbidities

Intervention
12-week double-blind
Patients=268

Pitolisant at 5mg, 10 mg or 20 mg per day.

Patients=201

Placebo (oral tablet)

Patients=67

Open-label period
40-week
Patients=236

Pitolisant at 5mg, 10 mg or 20 mg per day.

Patients from pitolisant group = 181

Patients from placebo group =55

Primary Endpoint: (Used in economic model) ESS between baseline and end of study treatment.

12 week results - HAROSA II (refused CPAP group)

Baseline characteristics

- Patients enrolled= 268

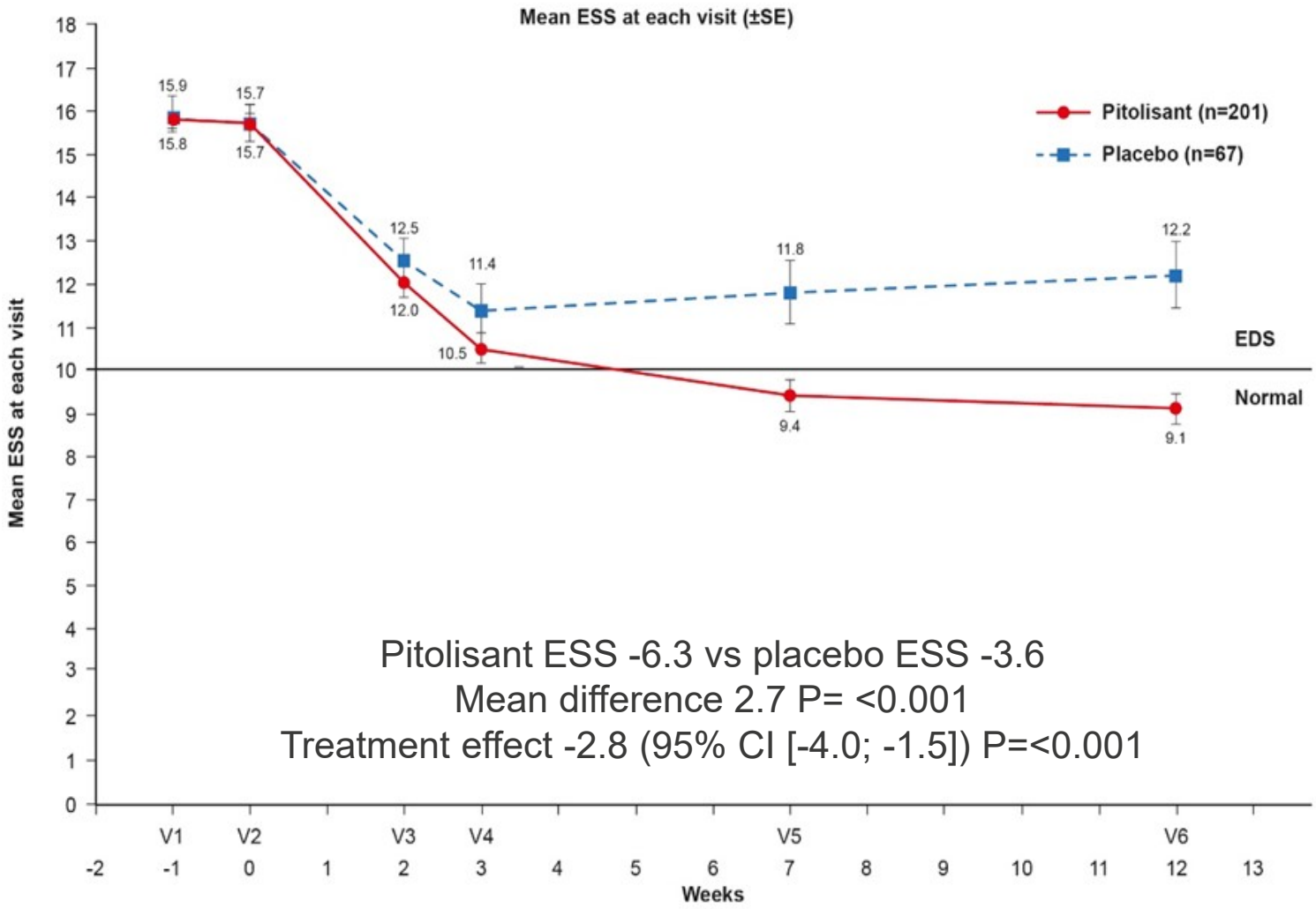
(201 pitolisant/ 67 placebo)

- Age (years) 51.9
- Male 75.1%
- BMI 32.8
- Professionally active 69.2%
- Working days per week 5.0
- CV history 54.7%
- ESS 15.7
- Pichot Fatigue scale 13

Statistical analysis

ANCOVA methodology and all tests were performed two sided at 5% level of significance.

ESS mean score (±SE) at each visit in the **12-week double-blind period**



Pitolisant ESS -6.3 vs placebo ESS -3.6
Mean difference 2.7 P= <0.001
Treatment effect -2.8 (95% CI [-4.0; -1.5]) P=<0.001

Pitolisant reduced daytime sleepiness with an ESS decrease of -6.30 in patients refusing CPAP.

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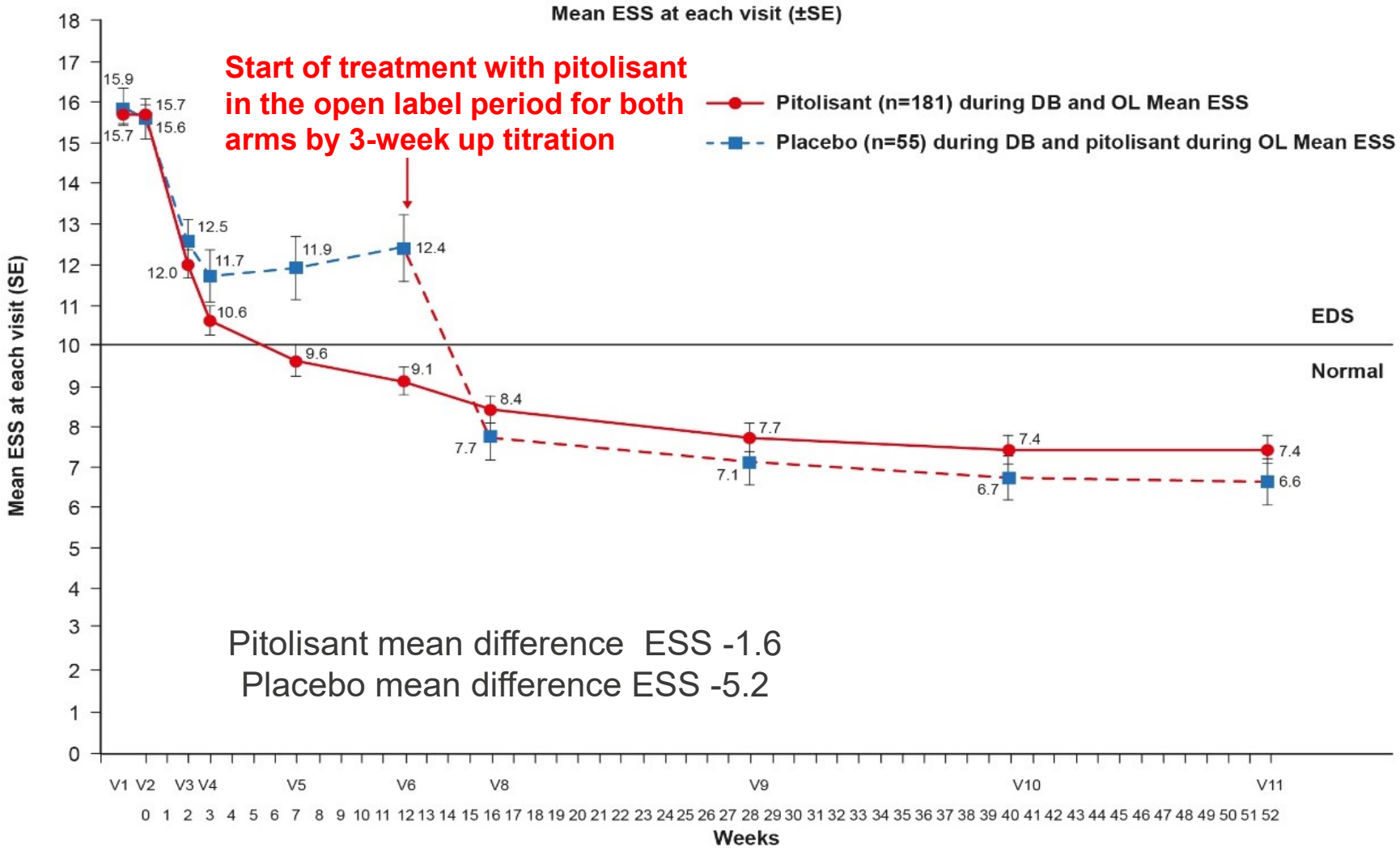
Overall results - HAROSA II (refused CPAP group)

ESS mean score (±SE) during the **overall study period**



By the end of the study period, patients who refused CPAP showed an ESS score within normal range of 7.7

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Results - HAROSA I & II (primary outcome)

Reduction in ESS, mean (SD), during the 12-week double-blind period

	Baseline	12 weeks (LOCF)	Baseline	12 weeks (LOCF)	Difference
HAROSA I	Pitolisant (n=183)		Placebo (n=61)		
	14.9 (2.7)	9.42 (4.66)	14.6 (2.8)	11.87 (5.70)	-5.52 (4.41) vs -2.75 (5.90) Mean difference: 2.77 p<0.001 Treatment effect of -2.6 (95% CI: [-3.9; -1.4]) (p<0.001)
HAROSA II	Pitolisant (n=201)		Placebo (n=67)		
	15.7 (3.1)	9.4 (4.6)	15.7 (3.6)	12.1 (5.8)	-6.3 (4.5) vs -3.6 (5.5) Mean difference: 2.7 p<0.001 Treatment effect of -2.8 (95% CI: [-4.0;-1,5]) (p<0.001)

Reduction in ESS, mean (SD), during the 40-week open-label period

	Entry into open-label	40 weeks (LOCF)	Difference	Entry into open-label	40 weeks (LOCF)	Difference
HAROSA I	Pitolisant then pitolisant (n=151)			Placebo then pitolisant (n=48)		
	9.4 (4.8)	8.1 (4.7)	-1.21 (3.12)	12.0 (6.0)	7.9 (5.1)	-4.07 (5.29)
HAROSA II	Pitolisant then pitolisant (n=181)			Placebo then pitolisant (n=55)		
	9.3 (4.6)	7.7 (4.5)	-1.6 (3.4)	12.2 (5.6)	7.0 (4.0)	-5.2 (5.4)

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Issues after technical engagement

Key Issues identified prior to technical engagement	Description of the issue	Impact	Status
1) Exclusion criteria of HAROSA I & II exclude patients with cardiovascular disease & psychiatric illness	Exclusion of these groups could impact the generalisability of the trial results		**Partially resolved**
2&3 Mandibular devices are relevant comparators for people who refuse CPAP and indirect treatment comparison reliability	Technical team considers that MAD are a relevant comparator and concerns regarding the ITC reliability		**Unresolved**
4) Insufficient follow up period	Uncertainty about whether the treatment effect will remain over a person's lifetime.		**Partially resolved**
5) Insufficient evidence of impact on cardiovascular events	Insufficient evidence that pitolisant would lead to a reduction in cardiovascular events		**Resolved**
6) Using mapping algorithm for utilities instead of direct utilities from HAROSA	Mc Daid et al algorithm instead of EQ-5D		**Partially resolved**
7) Insufficient evidence of effect on the probability of being involved in an road traffic collision	Uncertainty in considering a utility benefit of reducing road traffic accidents (RTA) when taking pitolisant.		**Partially resolved**
8) Placebo effect	Concerns regarding the need to adjust for placebo effect.		**Partially resolved**

Abbreviations: CPAP: continuous positive airway pressure MAD: mandibular advancement devices OSA: obstructive sleep apnoea RTA: Road traffic accidents

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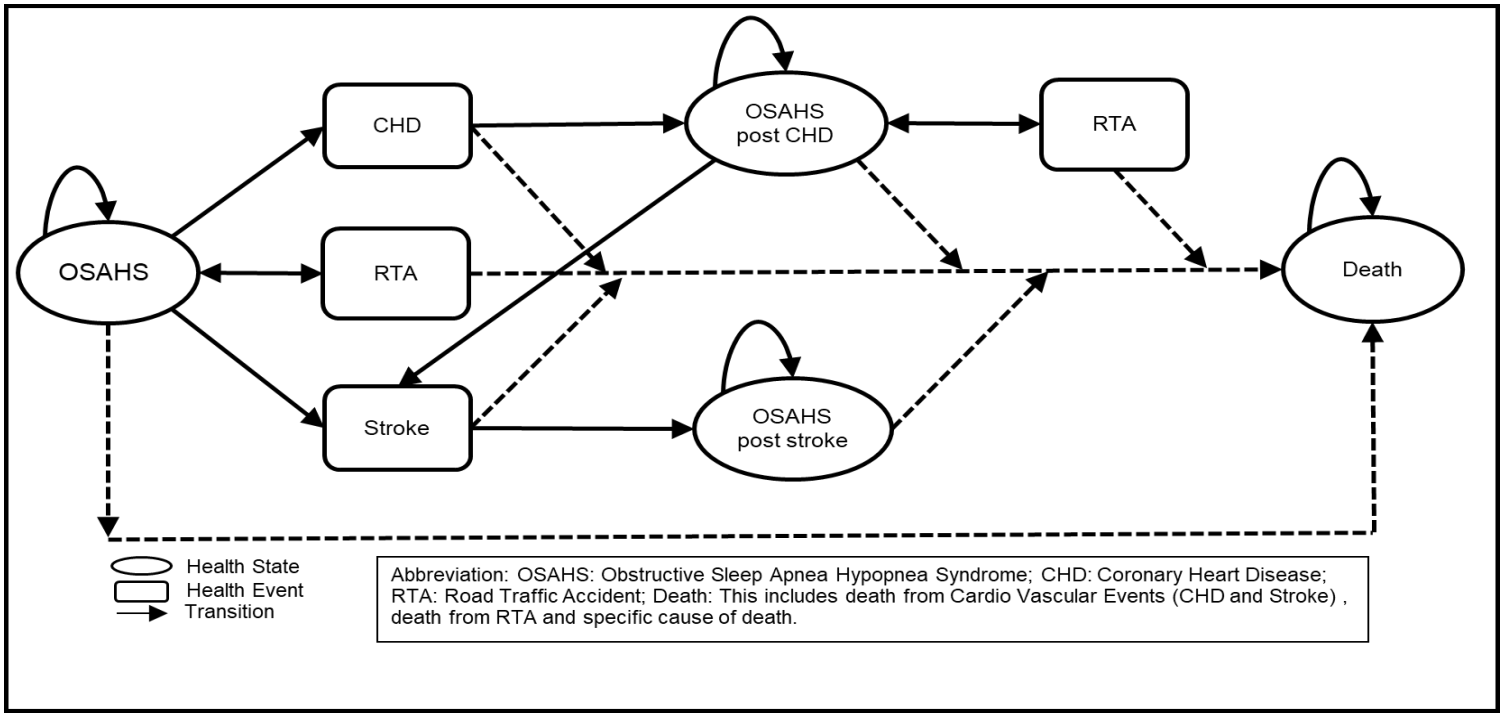
Key: Model driver;  Unknown impact;  Small/moderate impact 

Overview of company's model

Model characteristics

- Cohort-level state transition model
- 4 health states
- Annual cycle length
- Time horizon 25 years (revised at clarification)
- Costs, benefits discounted at 3.5% pa



Input	Data source
Clinical data	• HAROSA I (previous CPAP) & II (refused CPAP)
Treatment waning effect	• Lifetime effect • Assumed patients are on pitolisant for the rest of their life
Utilities	• Algorithm that allows mapping ESS to EQ-5D
Costs	• Lincoln Pharmaceutical pitolisant price • PSSRU 2019

Company's considerations of modelling

- Population: adult patients with OSA whose EDS has not been satisfactorily treated by primary OSA therapy.
- **Question: What change in ESS would constitute a clinically meaningful change?**
- At clarification the company acknowledged the ERG comments on the time horizon of 47 years as appropriate and agreed with their approach.
- Company states that is plausible that pitolisant may exert a benefit in reducing CV events but provided a scenario without this assumption.
- The company applied an absolute utility of 0.62 for both RTA [slight and severe].
- The company also applied an absolute utility of 0.77 for those experiencing stroke.

Summary

Comparators	CPAP and Mandibular advancement devices
Main clinical trials	HAROSA I, randomised controlled trial comparing people with moderate or severe obstructive sleep apnoea **who have used CPAP for at least 3 months** but still complain of excessive daytime sleepiness with placebo. N=244 HAROSA II, randomised controlled trial, comparing people with obstructive sleep apnoea **who refuse or cannot tolerate CPAP** with placebo. N=268
Key results	In those who previously used CPAP there was a reduction of -2.6 in ESS. 95% CI (-3.9; -1.4) p <0.001) In those who refused CPAP the reduction was of -2.8 in ESS. 95% CI (-4.0; -1.5) p <0.001)
Comparison of MAD with Pitolisant	The company presented an indirect treatment comparison in response to technical engagement. The results of it were inconclusive.
Economic Model	Markov model. 4 health states: obstructive sleep apnoea, post coronary heart disease, post stroke and death.
Company ICER	**People with residual EDS despite CPAP £29,698/QALY gained** **People with EDS due to OSA who refuse CPAP £29,803/QALY gained**
Technical team preferred ICER	**People with residual EDS despite CPAP £67,557/QALY gained** **People with EDS due to OSA who refuse CPAP £62,923/QALY gained**

Issue 1: Clinical evidence - Population in trials

Background

The exclusion criteria of HAROSA I and HAROSA II exclude patients with psychiatric illness and significant abnormality of the CV system (at the discretion of the investigator).

Company technical engagement response

- Comorbidities in people who have OSA is higher than the general population (Depressive disorders 15-56%; metabolic conditions 15-30%; CV 3 times higher)
- Patients with mild and moderate depression **were included** according BDI-13.

Pre-existing condition	HAROSA I	HAROSA II
Cardiovascular disease	56%	54%
Metabolic disorder	39%	30%
Psychiatric illness	18%	5%

Stakeholder technical engagement response

Clinical experts:

- Assumption of effectiveness cannot be extrapolated to patients that have not been studied. If this group of patients have not been in the trial, the efficacy on them is uncertain.
- Excluding people with psychiatric illness impacts the generalisability of the trial population to the NHS practice.

Comparator company: A meta-analysis by Garbarino et al. (2020) suggested that the prevalence of depressive symptoms in patients with OSA was 35% (95% CI, 28–41%).

ERG views after technical engagement

- The ERG checked the company's statements about the prevalence in these conditions in their submission and review their references.

- ***Is the population in the clinical trials generalisable to the NHS population?***

Issues 2 & 3 : Clinical evidence - Comparator

Background

MAD are relevant comparators in people with OSA who refuse CPAP. There are concerns regarding the reliability of the ITC of pitolisant with MAD.

Company technical engagement response

- MAD are not used in the same position in the treatment pathway → not a comparator
- An updated comparison showed no outcome differences from the original submission.
- Surface under the cumulative ranking curve (SUCRA) indicated that pitolisant was most likely to be the most effective treatment in both fixed effect and random effect analyses.

Stakeholder technical engagement response

Clinician:

- MAD and CPAP are the only devices available & very reliable. Use and access to MAD across the UK varies geographically. MAD: a good option in mild cases; would ***not*** prescribe pitolisant on this group as lifestyle measures and CPAP would be preferred.

Comparator company:

- MAD have been reported in meta-analyses to have a positive treatment effect with respect to OSA and compliance rates that may be higher than for CPAP.

ERG views after technical engagement

- ERG agrees that the results of the ITC comparing MADs with pitolisant are unreliable because the populations in the MAD trials do not match those in the pitolisant trials.

- ***Are mandibular devices a relevant comparator for pitolisant?***
- ***Is it appropriate to consider the indirect treatment comparison comparing MAD?***

Issue 4: Clinical evidence - Trial follow-up period

Background

- Double blind period in the trials lasted 12 weeks and open label extension for 40 weeks.

Company technical engagement response

- Pitolisant licensed for narcolepsy and evidence is available on efficacy and safety for >1 year.
- The HARMONY III (narcolepsy) has data for 1 year and xxxxxxxxxxxxxxxxxxxxxxx.
- A 5-year multi-centre, observational Post-Authorisation Safety Study (PASS) is documenting the use of pitolisant in patients with narcolepsy to collect information on its long-term safety when used in routine medical practice. xxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxx.

Stakeholder technical engagement response

Clinician: Clinicians said they have experience using pitolisant on patients with narcolepsy and commented that they could quickly see the benefits as well as the side effects. Agreed that the time is adequate to see the effects of pitolisant.

Comparator company: The data provided for pitolisant ranging to 1-year of follow up, it is likely that any pharmacologically-mediated waning of effect would have been apparent in that time.

ERG views after technical engagement

- The results of HARMONY III are encouraging nevertheless these results come from a small number patients with a different disease.
- ERG is not convinced that the same applies to pitolisant in obstructive sleep apnoea

- ***Would pitolisant have beneficial effects beyond the studied period?***

Issue 5: Cost effectiveness- Impact of cardiovascular events

Background

Insufficient substantiation of the impact of pitolisant on reducing CV events (CHD and stroke).

Company technical engagement response

- EDS is an independent risk factor for CV disease and pitolisant has been shown to reduce the magnitude of EDS caused by OSA.
- Company state that there is a reasonable circumstantial case to be made that pitolisant may exert a benefit in reducing CV events
- The magnitude of this effect is uncertain and they "would therefore request that this uncertainty be made clear to the committee and that a scenario analysis be presented, incorporating the CV benefit, to inform the discussion between the expert and lay members."

Stakeholder technical engagement response

Clinician: ESS is a generic measure of many things that cannot be used to link a cardiovascular effect. The evidence shows that there is reduction in BP levels after using CPAP.
Comparator company: Agree to remove CV benefit because modelling a utility benefit of this kind could suggest to patients or the clinical community that pitolisant alone improves cardiovascular outcomes.

ERG views after technical engagement

- There is neither direct nor indirect evidence that treatment with pitolisant has an effect on the incidence of CHD events and stroke
- The ERG agrees with the company's conclusion that there is good evidence for EDS as an independent risk factor for CV disease, and also with their statement that there is no evidence that a reduction of EDS will result in a reduction in CV risk.
- The lack of evidence to support that pitolisant is linked to a reduction in CV event led to the proposal of excluding this effect from the base-case analysis.

- ***Is it reasonable to exclude the utility benefit of reducing cardiovascular events?***

Issue 6: Cost effectiveness evidence – Mapping utilities

Background

Use of a mapping algorithm (McDaid et al) to populate the utility values of the health states in the model instead of the direct utility measurement in HAROSA trials.

Company technical engagement response

- Generic measures of QOL, such as the EQ-5D, do not capture benefits in patients with EDS because sleep is not included as a specific dimension.
- This is reflected in the EQ-5D results in the trials that showed that pitolisant did not have an impact on EQ-5D (no statistical difference between pitolisant and placebo in both trials).
- The regression models mapped from three data sets of individual patient data. Two that measured ESS and SF-36 and one that measured ESS, SF-36 and EQ-5D.
- EQ-5D mapping is used in the base case and SF-6D mapping in a scenario analysis.

Stakeholder technical engagement response

Clinician:

- EQ-5D would have been helpful but it does not capture improvements to sleepiness well. There are other QoL measures that are more appropriate to showing improvements.

Comparator company:

- The use of the McDaid et al algorithm is an appropriate methodology and has been used in previous NICE technology appraisals (TA139).

ERG views after technical engagement

- ERG requested a scenario analysis using utilities based on EQ-5D at clarification but this was not provided by the company because the underlying data was not available to them.
- The ERG agrees with the choice of the mapping algorithm of McDaid et al.in the company model.

- ***Is the mapping algorithm an acceptable approach to capture benefits?***

Issue 7: Cost effectiveness evidence – Utilities for RTAs

Background

Uncertainty in considering a utility benefit of reducing road traffic accidents (RTA) when taking pitolisant.

Company technical engagement response

- EDS has a significant impact on RTA (Meta analysis by Sassani et al 2004, suggested odds ratio of the risk of a collision in drivers with OSA was 2.52).
- No direct evidence of the impact of pitolisant on the occurrence of RTA.
- Reference to other methods to reduce daytime sleepiness in improving driving performance (solriamfetol, modafinil, CPAP)

Stakeholder technical engagement response

Clinician: Driving is the last thing to be considered when assessing quality of life. Being able to work and concentrate are a more important association in quality of life improvement.
Patient organisation: If the patient still experienced EDS with CPAP therapy, they should not be driving at all, so RTA would not occur unless the patient was breaking the law by driving whilst sleep impaired.
Comparator company: DVLA guidance states that patients whose EDS is not controlled must not drive until symptoms are under control and a patient is strictly following treatment

- Including RTAs in a population who are not allowed to drive overstates the benefits of pitolisant.

ERG views after technical engagement

- The ERG would have preferred direct evidence of the impact of pitolisant on RTA or at least on objective measures of poor driving.
- The ERG agrees with the company that it is reasonable to assume a similar association between RTA and objective measures of poor driving for pitolisant as with other methods to reduce EDS.

- ***Is it reasonable to consider a utility benefit of reducing RTA when taking pitolisant?***

Issue 8: Clinical evidence- Placebo effect

Background

- Potential for a placebo effect in the HAROSA I and II trials
- In recent ACD for solriamfetol (ID1499), the committee agreed in that case an adjustment for the placebo effect was needed but the methods used were associated with uncertainty.

ERG views

- The placebo effect showed minimal difference in ICERs even when using different assumptions such as the regression to the mean or centring.
- The company's model implicitly assumes a regression to the mean by using the ESS value at week 12. (Tendency for extreme values to move closer to the mean when measures are repeated over time.)
- ERG explored a centring assumption by using the ESS score at week 0. This is unlikely to impact the ICER.

- ***Is it appropriate to consider an adjustment for the placebo effect?***

Issues considered in other sleep apnoea appraisal – ACD solriamfetol for EDS caused by sleep apnoea (ID1499)

Issue	Description	Conclusion
Adherence	Patient experts and ERG raised the concern that some people with EDS would prefer to manage their symptoms with a drug treatment rather than primary therapy with CPAP leading to a reduction of the combined benefit of CPAP and solriamfetol.	Adherence to a primary therapy like CPAP is unlikely to be affected by treatment with solriamfetol, but more data are needed.
Hospitalisation	The company model did not include costs for serious adverse events because most adverse events in the clinical trial (TONES 3) were mild or moderate in severity.	Hospitalisation costs for serious adverse events should be included in the modelling.
Placebo effect	The improvement in ESS in the placebo + standard care group was a result of an observation bias (Hawthorne effect). The adjustment for this effect comprised removal of the improvements in ESS in the placebo arm from both placebo and solriamfetol groups in the model.	The adjustment for observation bias effect in its model was plausible although considerable uncertainty remains.
Partner utilities	Partner utilities were considered in a scenario analysis. ERG had concerns of the methods used to estimate the utility values because the time trade- off may not be comparable to those in EQ-5D.	Partner utility values are important to consider but it had not been presented with enough evidence to support its inclusion in the modelling.

Innovation and Equality considerations

Innovation

Comments from clinical expert submissions

- Innovative as there is no current treatment in this area so could have substantial benefit (which needs to be offset with the substantial infrastructure improvement needed)

Equalities issues

- People with neurodegenerative conditions or mental health issues with residual excessive daytime sleepiness could be discriminated against if the recommendations restricted pitolisant for use with CPAP only

Company and ERG base case preferred assumptions

Base-case preferred assumptions	Company	ERG	ERG justification for change
Time horizon	25 years (Company acknowledged 47 years is appropriate)	47 years	**Reflect a true lifetime horizon where patients can live up to an age of 100 years.**
Impact decline ESS	Decline ESS leads to decline risk of CVD	Decline ESS has no impact on risk of CVD	**No evidence was provided that a change in ESS would lead to changes in the risk of CHD and stroke**
Utility RTA	Absolute utility of 0.62	Utility decrement of 0.074	**The absolute utility of 0.62 was based on severe RTAs, while only 21% of the RTAs were severe. A utility decrement equal to stroke was assumed for slight RTAs. The weighted utility decrement for severe and slight RTAs was 0.074.**
Utility decrements ageing	Constant utility decrement of -0.0007	Age dependent utility decrement varying from -0.004 for 50-year olds to -0.007 for 100-year olds	**The equation of Ara and Brazier 2010 is used to account for the age-dependent decline in utility due to ageing.**

ERG = evidence review group; RTA = road traffic accident.; CVD = cardiovascular disease, CHD = coronary heart disease; ESS = Epworth Sleepiness Scale

Cost-effectiveness results – List price

Company's base-case cost effectiveness results

HAROSA I- People with residual EDS despite CPAP

Technologies	Total costs	Total QALYs	Incremental costs	Incremental QALYs	ICER (£/QALY)
Pitolisant + CPAP + BSC	£32,182	12.48	£21,061	0.71	£29,698
CPAP + BSC	£11,121	11.77			Probabilistic ICER £29,824

BSC = best supportive care; CPAP = continuous positive airway pressure;
ICER = incremental cost effectiveness ratio; QALYs = quality-adjusted life years.

HAROSA II - People with EDS due to OSA who refuse CPAP

Technologies	Total costs	Total QALYs	Incremental costs	Incremental QALYs	ICER (£/QALY)
Pitolisant + BSC	£30,923	12.57	£20,601	0.69	£29,803
BSC	£10,322	11.87			Probabilistic ICER £29,932

BSC = best supportive care; CPAP = continuous positive airway pressure; EDS = excessive daytime sleepiness;
ICER = incremental cost effectiveness ratio; OSA = obstructive sleep apnoea; QALYs = quality-adjusted life years.

Company's cost effectiveness results: Scenario analyses

Produced by ERG with the company's updated economic model after clarification.

	Scenario	ICER (£/QALY)	QALYs gained	+/- company base case
	Company base case HAROSA I	£29,698	0.71	Increment from BSC +£21,061
	HAROSA II	£29,803	0.69	Increment from BSC +£21,601
A	Comparison of pitolisant versus MAD in patients with EDS due to OSA who refuse CPAP (based on HAROSA II)	£51,445	0.29	+ £14,834
B	Use of SF-6D as the HRQOL instrument in the model HAROSA I	£34,034	0.62	+ £21,061
	HAROSA II	£34,534	0.60	+£20,601
C	Use of Framingham equation to estimate baseline CV risk. HAROSA I	£23,929	0.86	+£20,641
	HAROSA II	£22,516	0.88	+£19,820
D	Exclusion of costs and utilities of CV events from the model. HAROSA I	£77,241	0.37	+£28,555
	HAROSA II	£69,478	0.39	+£27,020

ERG's preferred model assumptions HAROSA I

Produced by ERG using the company's updated economic model and list price

Preferred assumption	Pitolisant + CPAP + BSC		CPAP + BSC		Inc. Costs (£)	Inc. QALYs	ICER (£/QALY)
	Total Costs (£)	Total QALYs	Total Costs (£)	Total QALYs			
Company base-case after clarification	32,182	12.48	11,121	11.77	21,061	0.71	29,698
Company base-case + errors corrected	33,567	11.98	8,942	11.17	24,625	0.82	30,173
ERG change 1: Time horizon	38,855	13.50	11,631	12.44	27,224	1.06	25,649
ERG change 2: No impact on CVD	30,663	12.41	2,108	11.91	28,555	0.50	57,647
ERG change 3: RTA disutility	33,567	12.00	8,942	11.26	24,625	0.74	33,340
ERG change 4: Age decrements	33,567	12.05	8,942	11.23	24,625	0.82	30,094
ERG base-case (changes 1-4)	35,043	14.28	2,416	13.80	32,626	0.48	67,557

BSC = best supportive care; CPAP = continuous positive airway pressure; CVD = cardiovascular disease; EDS = excessive daytime sleepiness; OSA = obstructive sleep apnoea; ICER = incremental cost effectiveness ratio; QALYs = quality-adjusted life years.

ERG's preferred model assumptions HAROSA II

Produced by ERG using the company's updated economic model and list price

Preferred assumption	Pitolisant + BSC		BSC		Inc. Costs (£)	Inc. QALYs	ICER (£/QALY)
	Total Costs (£)	Total QALYs	Total Costs (£)	Total QALYs			
Company base-case after clarification	30,923	12.57	10,322	11.87	20,601	0.69	29,803
Company base-case + errors corrected	31,707	12.05	7,845	11.25	23,862	0.80	29,928
ERG change 1: Time horizon	36,800	13.64	10,391	12.60	26,409	1.04	25,445
ERG change 2: No impact on CVD	29,795	12.57	2,416	12.05	27,378	0.52	52,777
ERG change 3: RTA disutility	31,707	12.06	7,845	11.36	23,862	0.71	33,808
ERG change 4: Age decrements	31,707	12.12	7,845	11.32	23,862	0.80	29,856
ERG base-case (changes 1-4)	34,752	14.76	2,827	14.26	31,925	0.51	62,923

BSC = best supportive care; CPAP = continuous positive airway pressure; CVD = cardiovascular disease; EDS = excessive daytime sleepiness; OSA = obstructive sleep apnoea; ICER = incremental cost effectiveness ratio; QALYs = quality-adjusted life years.

Key issues

ISSUE	KEY QUESTIONS
Issue 1: The exclusion criteria of HAROSA I and HAROSA II clinical trials exclude patients with cardiovascular disease and psychiatric illness.	• ***Is the population in the clinical trials transferable to the NHS population?***
Issue 2 & 3: Mandibular devices are a relevant comparator in people with OSA who refuse CPAP and concerns of the ITC reliability	• ***Are mandibular devices a relevant comparator for pitolisant?*** • ***Is it appropriate to consider the indirect treatment comparison comparing MAD?***
Issue 4: Insufficient follow up period	• ***Would pitolisant have beneficial effects beyond the studied period?***
Issue 5: Insufficient substantiation of the impact of pitolisant on reducing cardiovascular events	• ***Is it reasonable to exclude the utility benefit of reducing cardiovascular events?***
Issue 6: Use of a mapping algorithm for utilities instead of the direct utility measurement in the HAROSA I and II trials.	• ***Is the mapping algorithm an acceptable approach to capture benefits?***
Issue 7: Insufficient evidence of a direct effect of pitolisant on the probability of being involved in an RTA.	• ***Is it reasonable to consider a utility benefit of reducing RTA when taking pitolisant?***
Issue 8: Placebo effect	• ***Is it appropriate to consider an adjustment for the placebo effect?***