Controverse :

Faut-il se contenter de traiter un symptôme dans la prise en charge de la somnolence diurne résiduelle chez un SAOS ?

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- **Liens d’intérêt :**

  - AstraZeneca, GSK, Chiesi, Novartis, Bayer, MSD,
  - Bastide, SOS oxygène, Elivie, Elia medical
  - Philips Ultrasons, Lowenstein

SAHOS en France

- En France: **entre 3% et 10% de la population adulte** avec SAOS soit environ **2.5 à 6.5 millions de Français.**
- **Plus de 50% des apnéiques pas encore diagnostiqués.**
- **Seulement 20% à 30%** des malades sont **pris en charge** en France
  - nombre de patients traités **par PPC > 1 200 000 en 2020**
  - nombre de patients traités par OAM 15 000 patients en 2017

1- Données 2015 - https://www.sfrms-sommeil.org/recherche/actualite-scientifique/communique-saos-le-bon-traitement-pour-le-bon-patient/
2- Avis transparence Solriamfetol 2020
3-*HAS AVIS DE LA CNEDiMTS 21 mai 2019*
https://www.has-sante.fr/upload/docs/evamed/CNEDIMTS-5854_ONIRIS%20PRO_21_mai_2019_(5854)_avis.pdf

Somnolence dans SAHOS

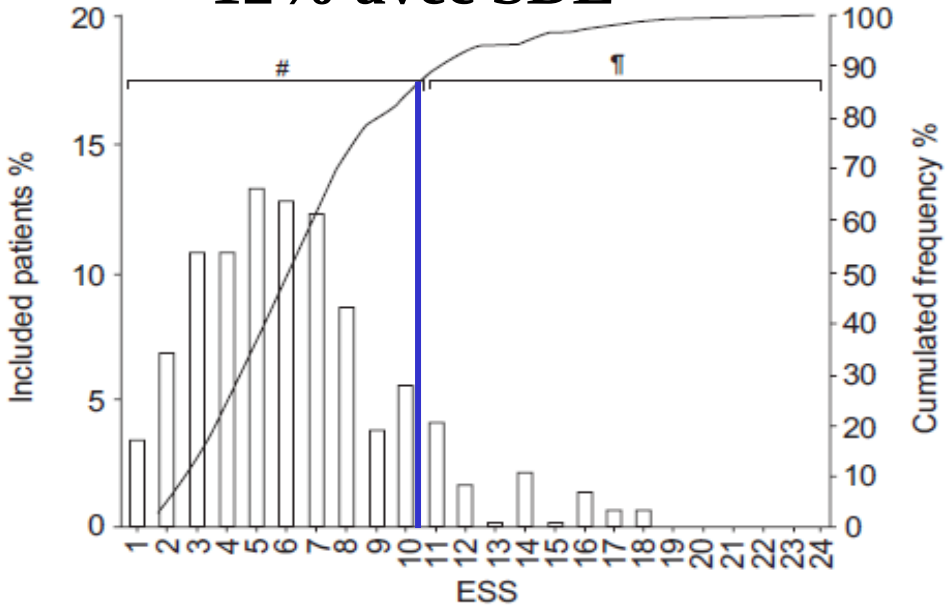
- ✓ SDE touche environ 12% de la population générale
- ✓ 19% SDE dans SAHOS selon data du Wisconsin Sleep Cohort study
- ✓ SDE < 50% dans une étude rétrospective USA avec SAHOS modéré à sévère.
- ✓ Jusqu'à 60% de patients d'âge moyen avec SDE dans une étude conduite en Europe
- ✓ SDE de 87.2% parmi patients avec SAHOS en Asie selon une étude rétrospective

Gabarino et al . Obstructive Sleep Apnea With or Without Excessive Daytime Sleepiness: Clinical and Experimental Data-Driven Phenotyping. Frontiers in Neurology. 2018. 9. 505

Somnolence résiduelle dans SAHOS

- 502 patients
- IAH< 10 et PPC > 3H/J
- Exclusion : travail posté , privation sommeil , autre pathologie chronic

12% avec SDE



Puis après élimination de:

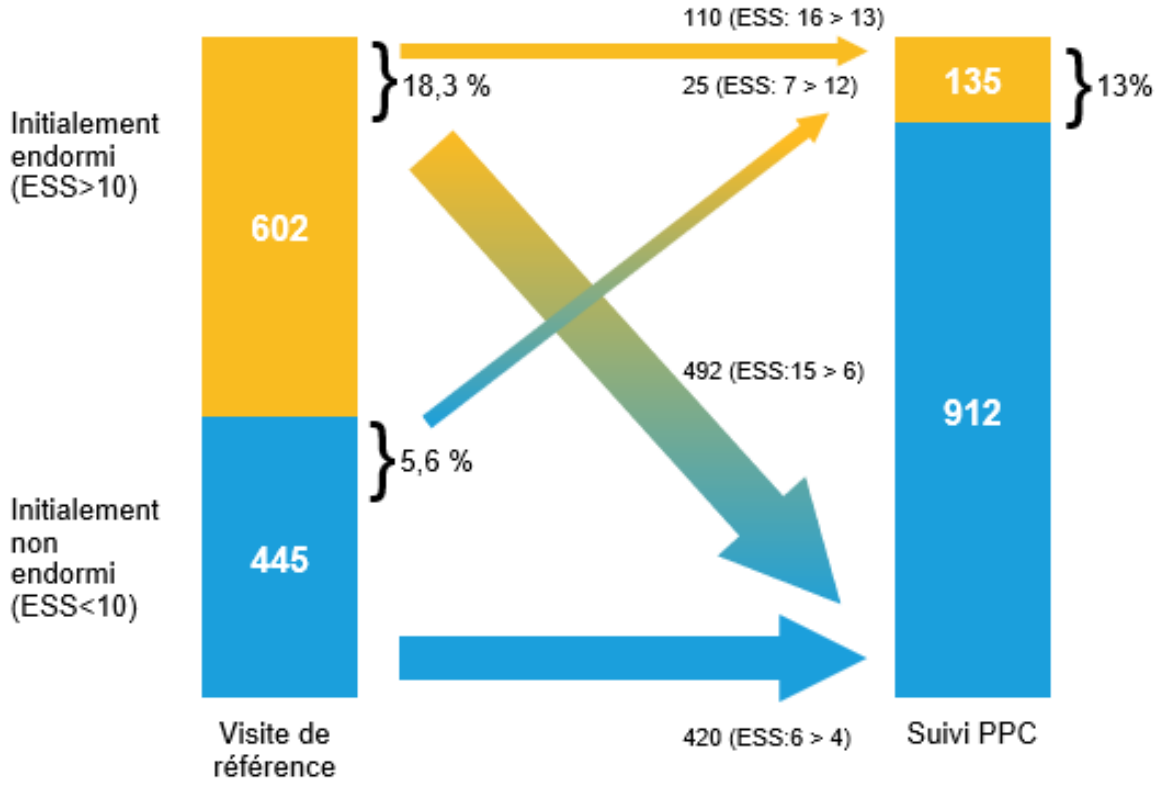
- SJSR 25%
- Dépression 17%
- narcolepsie 2%

→ Prévalence 6% SDE résiduelle

Pepin Prevalence of residual excessive sleepiness in CPAP-treated sleep apnoea patients: the French multicentre study Eur Respir J 2009; 33: 1062–1067

Somnolence résiduelle dans SAHOS

1 047 patient sous PPC suivis entre 3 mois et 2 ans



- Baseline avant PPC :

602 patients (57 %) avec ESS>10

- Après 3 à 24 mois

sous PPC(>3h/nuit) :
135 patients (13 %) sont somnolents

- 18,3 % des patients somnolents

au diagnostic le restent (110/602)

- 5,6 % (25/445) des patients

non somnolents au diagnostic

le deviennent

Gasa &Al Residual sleepiness in sleep apnea patients treated bycontinuous positive airway pressure J Sleep Res. (2013) 22, 389–397DOI: 10.1111/jsr.12039

Comorbidités SAHOS et somnolence

Table 2 Characteristics at diagnosis according to the presence of RES at follow-up

	RES+(n = 135, 13%)	*RES−(n = 912, 87%)*	*P-value*
Anthropometrics			
Age (years)	56.12 ± 11.55	57.56 ± 12.57	0.0909
Male/female (%)	60/40	71/29	**<0.01**
BMI (kg m^{-2})	31.14 ± 6.11	32.08 ± 6.65	NS
Subjective scale values at baseline			
ESS	14.17 ± 4.65	10.91V5.06	**<0.0001**
Depression	4.14 ± 3.91	3.08 ± 3.35	**<0.01**
Fatigue	14.50 ± 9.09	11.18 ± 7.91	**<0.0001**
General health	5.22 ± 2.39	5.98 ± 2.45	**<0.001**
Co-morbidities			
Hypertension (%)	45.19	50.55	NS
Arrhythmia (%)	8.15	8.44	NS
Stroke (%)	1.48	3.18	NS
Heart failure (%)	2.96	1.71	NS
Peripheral arterial disease (%)	2.22	1.97	NS
Ischaemic cardiomyopathy (%)	6.67	7.68	NS
Diabetes (%)	14.1	17.4	NS
PLM treatment (%)	0.74	0.33	NS
OSA severity			
Baseline AHI (events h^{-1})	40.60 ± 20.61	42.95 ± 19.45	**<0.05**
Oxygen desaturation index (nb h^{-1})	31.71 ± 23.22	34.99 ± 22.87	NS

Data expressed as mean ± standard deviation for continuous variables, and as a percentage for categorical variables. Test used: Student's *t*-test or Mann–Whitney test when appropriate for continuous variables; Chi-squared test or Fisher test when appropriate for categorical variables.
AHI, apnea–hypopnea index; BMI, body mass index; ESS, Epworth Sleepiness Scale; OSA, obstructive sleep apnea; PLM, periodic leg movement syndrome; RES, residual excessive sleepiness. *P* values in bold are statistically significant.

There was no relationship between residual excessive sleepiness

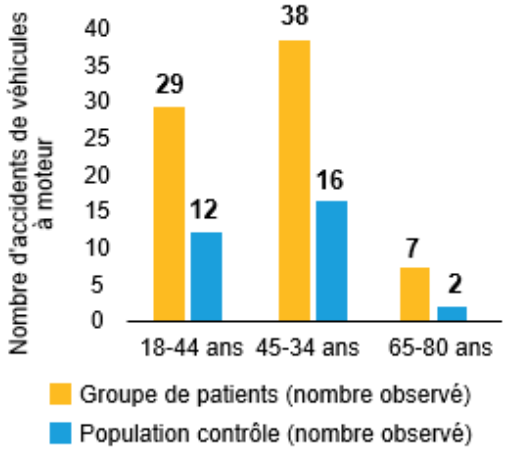
- body mass index
- cardiovascular co-morbidities
- or diabetes.

Gasa &Al Residual sleepiness in sleep apnea patients treated bycontinuous positive airway pressure J Sleep Res. (2013) 22, 389–397DOI: 10.1111/jsr.12039

Conséquences de somnolence: accidents de la route, accidents professionnels

Tableau 3. Conséquences des apnées du sommeil.

Conséquences	Magnitude (odds ratio)	Référence
Neurocognitives		
Accidents de la route	7,0	Teran-Santos [7]
Accidents professionnels	2,2	Lindberg [6]



Augmentation du risque d'accidents dans la population avec SAOS:

Risk Ratio : 2.5 (P < 0.001)

1-Heinzer 2007 Le syndrome d'apnées obstructivesdu sommeil Forum Med Suisse 2007;7:686–691
2- Kamiri M, et al. Swedish Traffic Accident Registry Data. Sleep. 2015;38(3):341–9.

Dépistage et évaluation de la somnolence diurne excessive

La somnolence diurne excessive (SDE) se caractérise par une somnolence persistante, un manque de vigilance et souvent un manque d'énergie général, même pendant la journée.

- **ÉVALUATION SUBJECTIVE (auto-test réalisé par le patient lui-même) :**
  - L'échelle de somnolence d'Epworth (ESS) qui compile les résultats d'un questionnaire est la plus utilisée.
- **ÉVALUATIONS OBJECTIVES (souvent en centre du sommeil)**
  - Le Test Itératif de Latence à l'Endormissement (TILE)
  - Le Test de Maintien de l'Eveil (TME) : test légal
  - Le Test d'Osler : le plus simple à réaliser mais peu utilisé

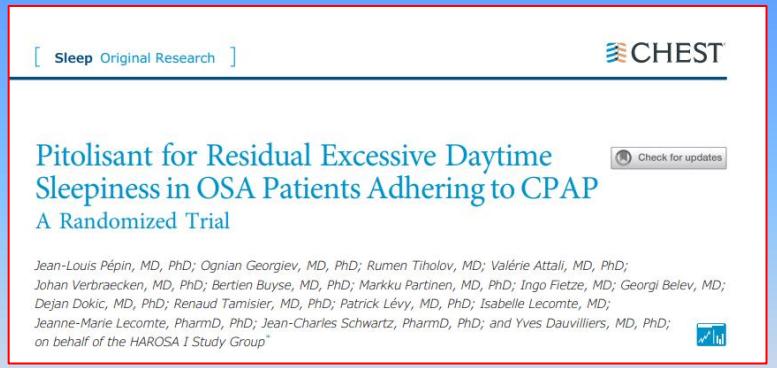
1. Recommandations pour la pratique clinique du syndrome d'apnées hypopnées obstructives du sommeil de l'adulte, Revue des maladie respiratoires, 2010, https://www.sfrms-sommeil.org/wp-content/uploads/2012/10/HS3_reco_sas2010-1.pdf p22

Prise en charge de la SDE dans SAHOS

- **Optimiser le traitement par PPC :**
  - Adapter la pression , limiter les fuites
  - Optimiser la compliance à la PPC

- **Identifier toute cause classique de SDE**
  - Autre pathologie sommeil : insomnie, narcolepsie, SJSR…
  - Eliminer une dette de sommeil (consciente ou non)
  - Troubles psychiatriques: dépression…
  - Prise médicamenteuse : BZD, Anti H1…

Somnolence résiduelle : 6-10%



[Sleep Original Research]

CHEST

Pitolisant for Residual Excessive Daytime Sleepiness in OSA Patients Adhering to CPAP

A Randomized Trial

Check for updates

Jean-Louis Pépin, MD, PhD; Ognian Georgiev, MD, PhD; Rumen Tiholov, MD; Valérie Attali, MD, PhD; Johan Verbraecken, MD, PhD; Bertien Buyse, MD, PhD; Markku Partinen, MD, PhD; Ingo Fietze, MD; Georgi Belev, MD; Dejan Dokic, MD, PhD; Renaud Tamisier, MD, PhD; Patrick Lévy, MD, PhD; Isabelle Lecomte, MD; Jeanne-Marie Lecomte, PharmD, PhD; Jean-Charles Schwartz, PharmD, PhD; and Yves Dauvilliers, MD, PhD; on behalf of the HAROSA I Study Group*

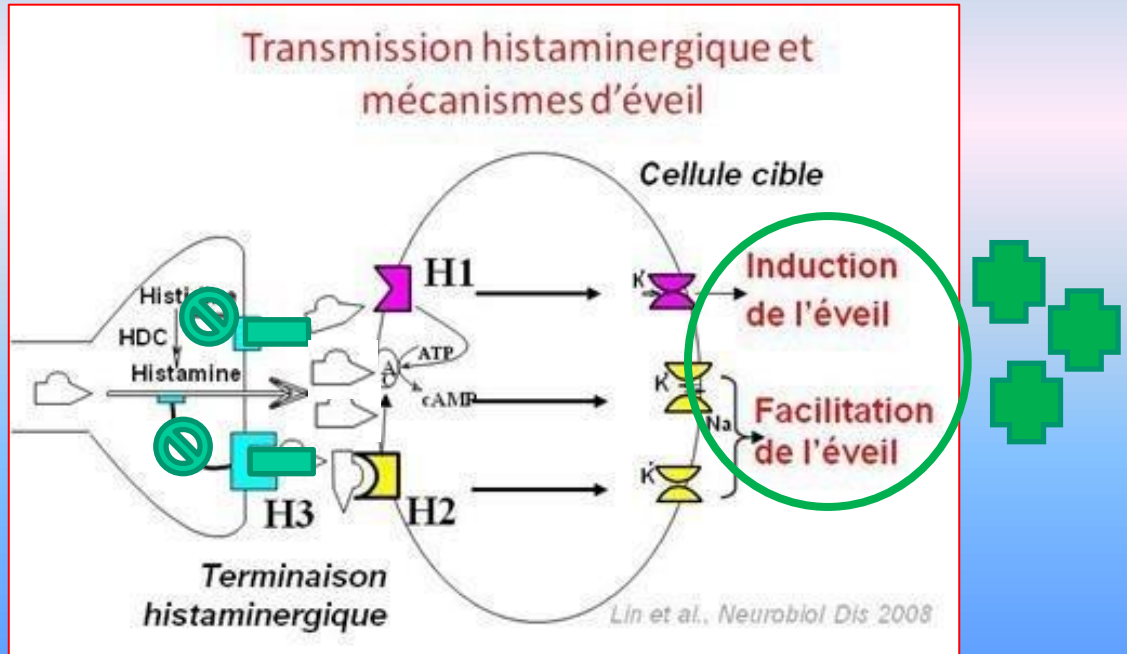
Phase 3 ; double aveugle ; vs placebo ; grp parallèles ; multicentrique

➔ Le Pitolisant est-il efficace pour réduire la somnolence diurne des patients avec un SAOS modéré à sévère, ayant une bonne observance de leur PPC

➔ Le profil de sécurité est-il acceptable ?

Pitolisant

- AMM (2016, WAKIX) : narcolepsie
- Antagoniste du récepteur H3 de l'histamine.



POPULATION D'ETUDE

- Critères d'inclusion:
- SAOS modéré à sévère (IAH ≥ 15)
- Observance PPC ≥ 4h/nuit + depuis ≥ 3 mois
- Somnolence diurne persistante (Epworth ≥ 12)
- IAH résiduelle < 10

- Critères de non inclusion:
- ATCD insomnie, SJSR
- Travail de nuit
- Chirurgie vélo-amygdalienne, OAM
- Comorbidité cardiovasculaire sévère
- Pathologie psychiatrique

Critères de Jugement

1) **Epworth** *inclusion* – **Epworth** *à 12 semaines*

2) **Oxford Sleep Resistance Test (OSleR)** *inclusion* – **OSleR** *à 12 semaines*

   Proportion de répondeurs

   Nombres d'épisodes de somnolence/siestes (carnet)

   Impression clinique du médecin

   Impression subjective du patient

OXFORD SLEEP RESISTANCE TEST (OSleR)

Tests objectifs de vigilance: OSleR

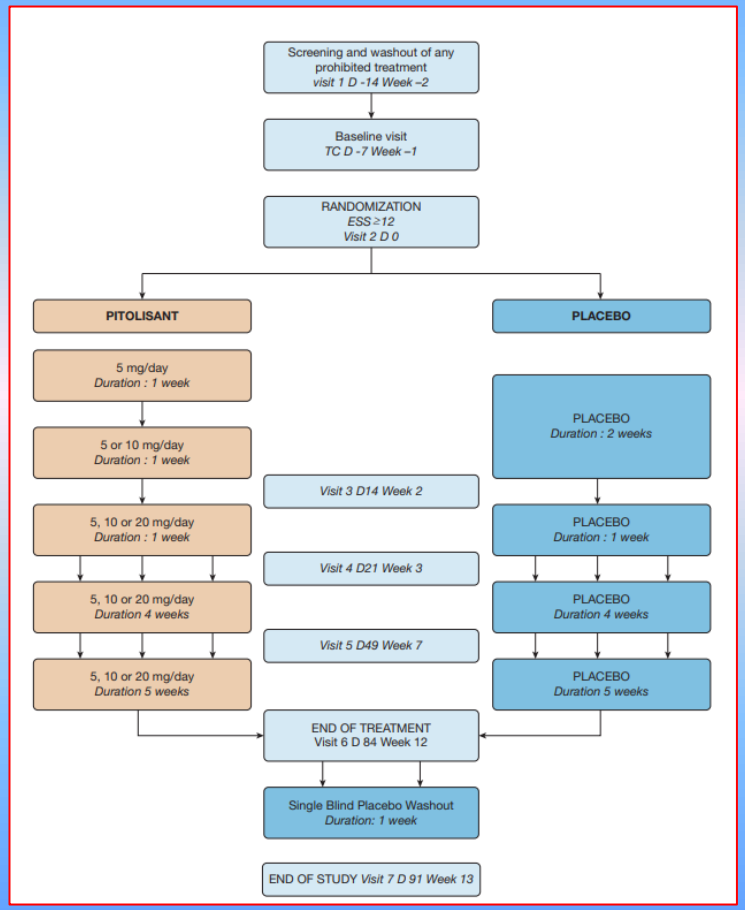
Somnolence objective + inattention

- Oxford Sleepiness Resistance Test (TME «comportemental»)
- Durée: 40 minutes x 3
- Arrêt si 7 erreurs consécutives
- Données recueillies
  - latence d'endormissement
  - profil d'erreurs

Consigne:
Appuyer sur un bouton en réponse à une stimulation lumineuse

Pitolisant for Residual Excessive Daytime Sleepiness in OSA Patients Adhering to CPAP

A Randomized Trial



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Pitolisant for Residual Excessive Daytime Sleepiness in OSA Patients Adhering to CPAP

A Randomized Trial

Check for updates

TABLE 1] Baseline Characteristics

Parameter	Pitolisant (n = 183)	Placebo (n = 61)	All Participants (N = 244)
Age, y			
Mean ± SD	53.8 ± 10.5	51.0 ± 10.6	53.1 ± 10.6
Range	23-81	25-72	23-81
Sex			
Male	149 (81.4)	53 (86.9)	202 (82.8)
Female	34 (18.6)	8 (13.1)	42 (17.2)
Weight at inclusion, kg	98.3 ± 18.8	97.9 ± 14.6	...
BMI, kg/m^2	32.7 ± 5.2	32.2 ± 4.3	...
Time since diagnosis, mo	44.8 ± 44.1	49.0 ± 57.1	45.9 ± 47.6
AHI with CPAP, number/h of sleep	4.1 ± 3.5	4.5 ± 3.1	4.2 ± 3.5
CPAP pressure, cm H_2O	10.7 ± 2.7	10.7 ± 3.0	10.7 ± 2.8
History of cardiovascular disease	111 (60.7)	27 (44.3)	138 (56.6)

Data are presented as No. (%), mean ± SD, or range. AHI = Apnea Hypopnea Index.

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Pitolisant for Residual Excessive Daytime Sleepiness in OSA Patients Adhering to CPAP

A Randomized Trial

TABLE 2 Efficacy Results for the Primary End Point: Change in ESS Score

Parameter	Pitolisant (n = 183)	Placebo (n = 61)	*P* Value
ESS score at inclusion	14.9 ± 2.7	14.6 ± 2.8	…
ESS score at end of treatment	9.0 ± 4.8	12.1 ± 6.1	…
Final ESS score DB-LOCF			< .001
Mean ± SD	9.4 ± 4.6	11.9 ± 5.7	
95% CI	8.8 to 10.1	10.4 to 13.3	
Change in ESS score (DB-LOCF - inclusion)			< .001
Mean ± SD	−5.5 ± 4.4	−2.7 ± 5.9	
95% CI	−6.2 to −4.9	−4.3 to −1.24	
ESS score ≤ 10			.028
No. (%)	103 (56.3)	26 (42.6)	
95% CI	48.8% to 63.6%	30.0% to 55.9%	
EES score ≤ 10 or reduction in EESS ≥ 3			.013
No. (%)	130 (71)	33 (54.1)	
95% CI	63.9% to 77.5%	40.8% to 66.9%	

Data are presented as No. (%), mean ± SD, or 95% CI, unless otherwise indicated. DB-LOCF = database with last observation carried forward; ESS = Epworth Sleepiness Scale.

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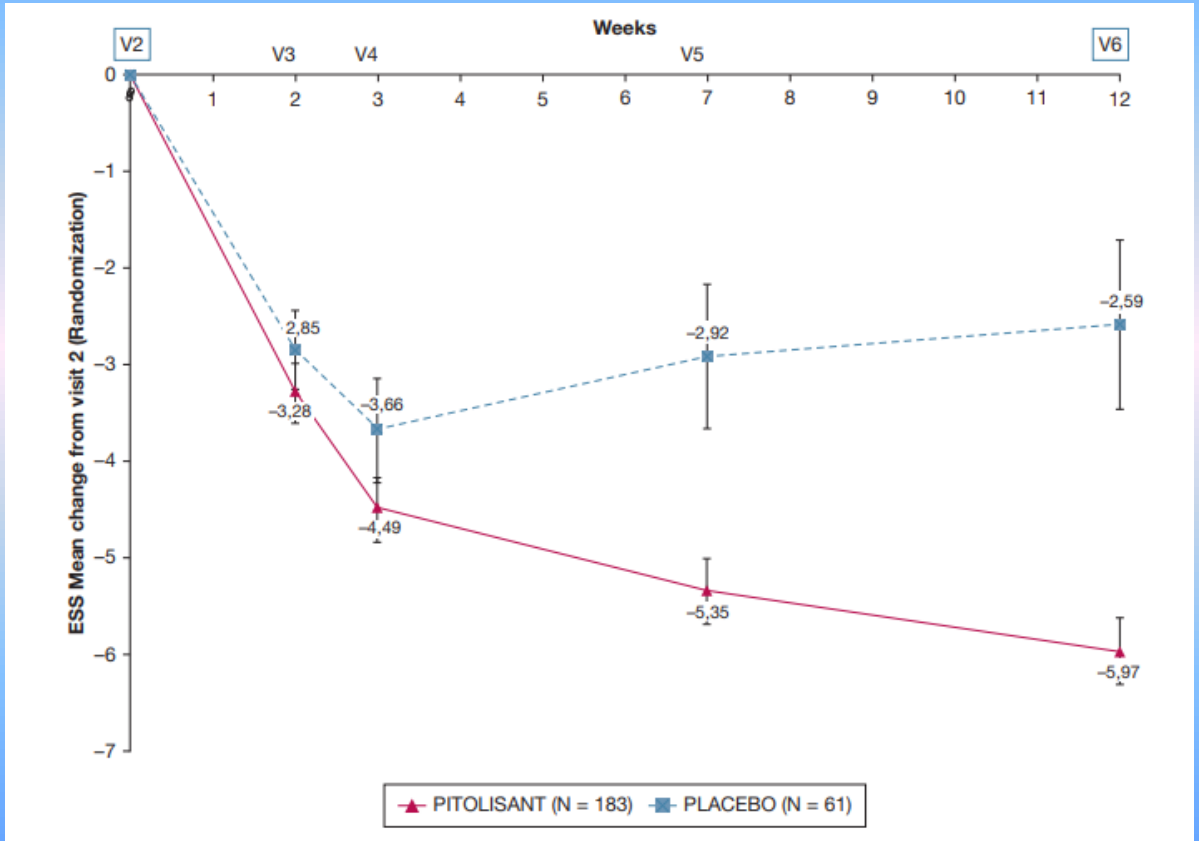
Pitolisant for Residual Excessive Daytime Sleepiness in OSA Patients Adhering to CPAP

A Randomized Trial



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Secondary endpoints

TABLE 3 Efficacy Results for Secondary Outcomes

Parameter	Pitolisant (n = 183)	Placebo (n = 61)	*P* Value
OSIeR test			
Sleep latency at inclusion, min	15.5 (0.3-40.0)	18.9 (0.7-40.0)	...
Sleep latency at end of treatment, min	22.3 (1.3-40.0)	21.9 (0.7-40.0)	...
Ratio OSL at visit 6 to OSL at visit 2 (geometric mean)	1.44	1.22	.05
Sleep diary variables			
Change in no. of sleep or sleepiness episodes per day	−2.1 ± 1.8	−1.34 ± 1.7	.06
Change in duration of sleep or sleepiness episodes, min/d	−51.8 ± 69.3	−47.7 ± 66.9	.70
Pichot fatigue score, change	−3.8 ± 5.6	−2.9 ± 5.9	.70
Leeds Sleep Evaluation Questionnaire			
Change in ease of getting to sleep	8.4 ± 20.8	0.7 ± 23.7	.02
Change in quality of sleep	9.9 ± 26.6	15.2 ± 21.9	.05
Change in ease of awaking after sleep	12.1 ± 24.8	12.0 ± 26.2	.81
Change in behavior after wakening	15.7 ± 21.8	15.7 ± 22.7	.37
Change in global score	11.6 ± 14.8	10.9 ± 14.9	.78
Trail Making Test			
Part A: change in average time, s	−5.9 ± 13.0	−6.2 ± 13.3	.88
Part B: change in average time, s	−11.7 ± 37.0	−15.3 ± 34.4	.45
EQ-5D change in VAS score	5.5 ± 14.9	3.5 ± 18.9	.52
Clinical Global Impression	136 (78.0)	31 (53.4)	< .001
95% CI	71.1%-84.0%	39.9%-66.7%	...
Very much improved	19 (11.0)	4 (6.9)	.005
Much improved	73 (42.2)	16 (27.6)	
Minimally improved	43 (24.9)	11 (19.0)	
No change	33 (19.1)	18 (31.0)	
Minimally worse	5 (2.9)	8 (13.8)	
Much worse	0 (0.0)	1 (1.7)	
Patient global opinion improvement at end of double-blind treatment			
No. (%)	133 (76.4)	33 (56.9)	
95% CI	69.4%-82.5%	43.2%-69.8%	

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Safety

TABLE 4 Safety Parameters

Parameter	Pitolisant (n = 183)	Placebo (n = 61)	*P* Value
Any TEAE	86 (47.0)	20 (32.8)	.030
Treatment related	49 (26.8)	12 (19.7)	.256
Serious	2 (1.1)	0 (0.0)	.998
Leading to study drug withdrawal	4 (2.2)	2 (3.3)	.625
Systolic BP			
Baseline (V2)	129.3 ± 12.9	130.2 ± 11.8	...
Range	100 to 180	110 to 163	...
End of DB treatment (V6)	128.7 ± 12.0	129.1 ± 12.0	...
Range	98 to 188	110 to 166	...
Change (SD)	−0.6 ± 10.1	−1.8 ± 10.1	.704
Range	−50 to 25	−20 to 33	
Diastolic BP			
Baseline (V2)	80.3 ± 8.9	80.6 ± 6.9	...
Range	56 to 109	59 to 96	...
End of DB treatment (V6)	79.9 ± 8.3	81.4 ± 9.0	...
Range	52 to 105	67 to 114	...
Change (SD)	−0.4 ± 7.3	0.6 ± 9.0	.228
Range	−25 to 20	−18 to 30	
Heart rate			
Baseline (V2)	70.9 ± 11.9	71.3 ± 9.6	...
Range	40 to 107	46 to 91	...
End of DB treatment (V6)	70.0 ± 11.5	70.3 ± 10.4	...
Range	43 to 115	39 to 96	...
Change (SD)	−0.9 ± 9.6	−1.4 ± 9.1	.845
Range	−25 to 29	0	
Total 13-item BDI score			
Baseline (V2)	4.5 ± 3.5	4.0 ± 3.4	...
95% CI	4.0 to 5.0	3.1 to 4.8	...
End of DB treatment (V6)	3.3 ± 3.2	2.8 ± 3.1	...
95% CI	2.9 to 3.8	2.0 to 3.7	...
Change between baseline and end of DB treatment	−1.2 ± 2.4	−1.2 ± 2.0	.516
95% CI	−1.5 to −0.8	−1.8 to −0.7	...

Data are presented as No. (%), range, mean ± SD, or 95% CI, unless otherwise indicated. BDI = Beck Depression Inventory; DB = double-blind; TEAE = treatment-emergent adverse event; V2 = visit 2; V6 = visit 6.

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Pitolisant for Residual Excessive Daytime Sleepiness in OSA Patients Adhering to CPAP
A Randomized Trial

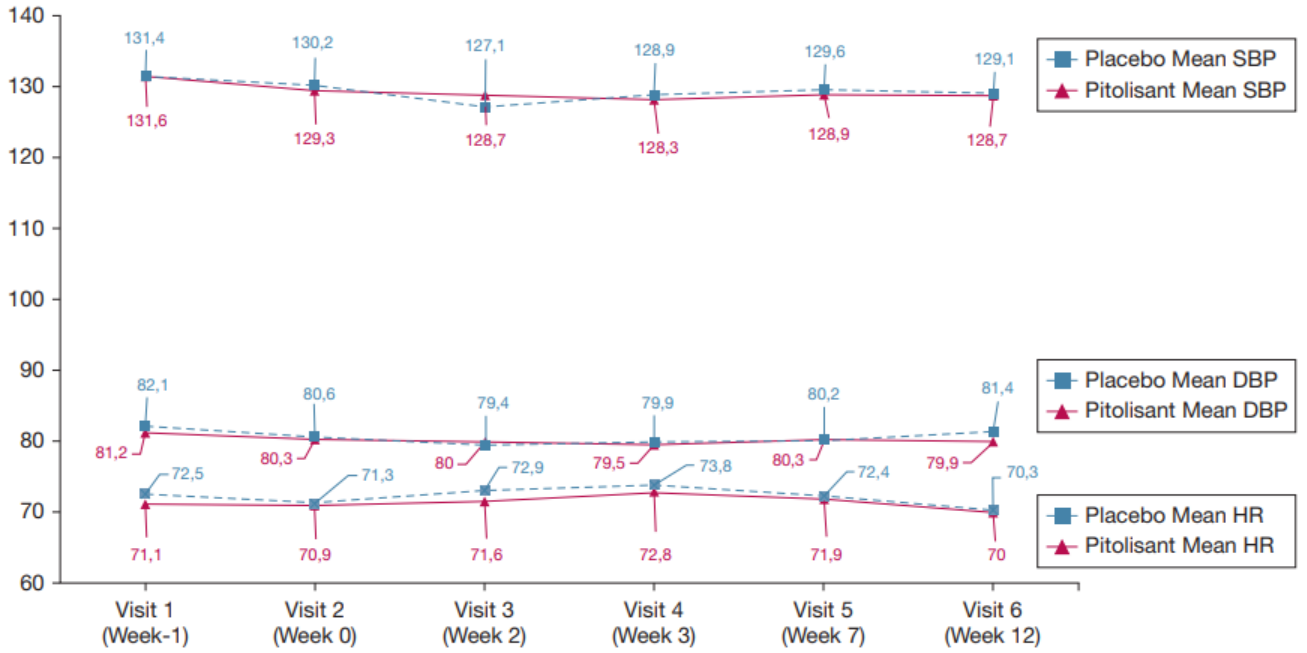


Figure 4 – *Line graph showing HR, SBP, and DBP in the pitolisant and placebo groups over the 12-week double-blind phase. DBP = diastolic BP; HR = heart rate; SBP = systolic BP.*

- Modafinil: AMM suspendue (↗ PAS 3 mmHg et PAD 2 mmHg)
- Solriamfetol: AMM mais CI si HTA non contrôlée (↗ PAS 2,5 mmHg et PAD 1,5 mmHg et 3 bpm)

Pepin JL et al. Chest 2021

Pitolisant for Daytime Sleepiness in Patients with Obstructive Sleep Apnea Who Refuse Continuous Positive Airway Pressure Treatment

A Randomized Trial

Yves Dauvilliers[1,2], Johan Verbraecken[3,4], Markku Partinen[5,6], Jan Hedner[7], Tarja Saaresranta[8,9], Ognian Georgiev[10], Rumen Tiholov[11], Isabelle Lecomte[12], Renaud Tamisier[13,14], Patrick Lévy[13,14], Catherine Scart-Gres[12], Jeanne-Marie Lecomte[12], Jean-Charles Schwartz[12], and Jean-Louis Pépin[13,14]; on behalf of the HAROSA II Study Group

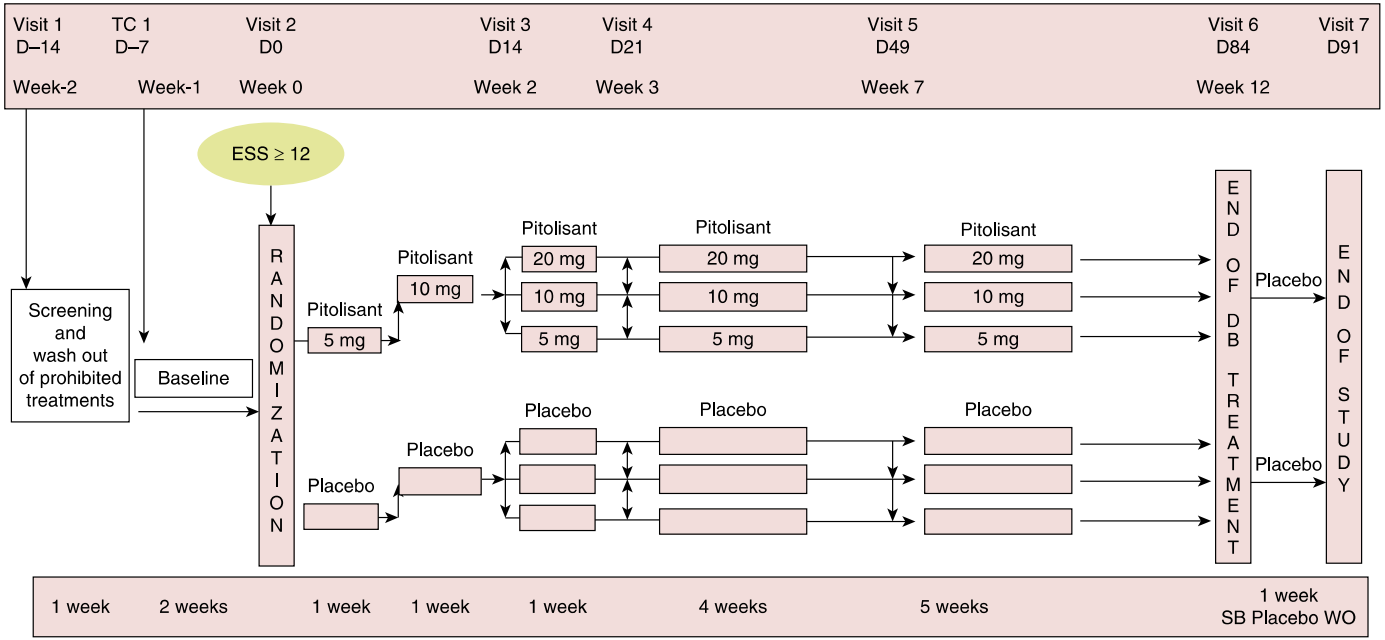
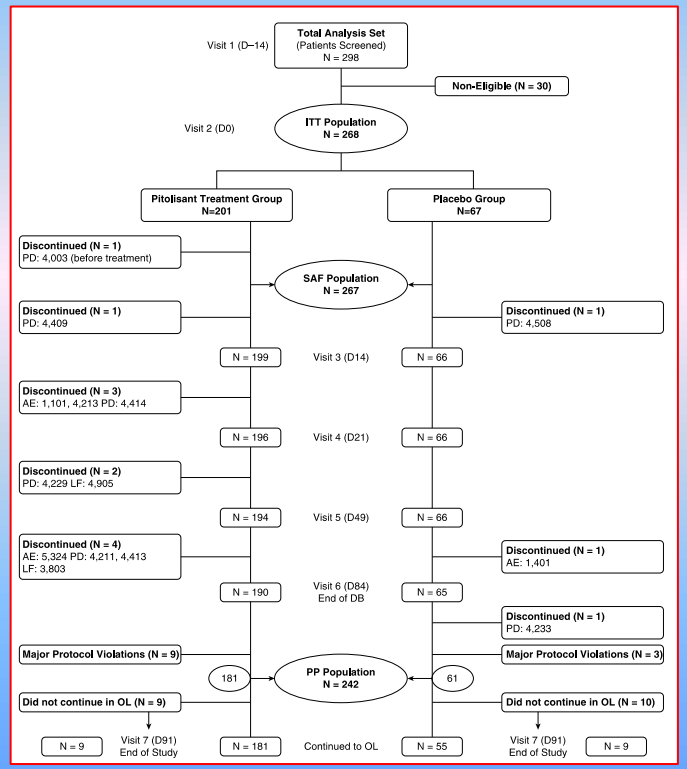


Figure 1. Study design. D = day; DB = double-blind; ESS = Epworth Sleepiness Scale; SB = single blind; TC = telephone call; WO = wash out.

Am J Respir Crit Care Med 2020; 201: 1135–1145.

Pitolisant for Daytime Sleepiness in Patients with Obstructive Sleep Apnea Who Refuse Continuous Positive Airway Pressure Treatment

A Randomized Trial



Am J Respir Crit Care Med 2020; 201: 1135–1145.

Pitolisant for Daytime Sleepiness in Patients with Obstructive Sleep Apnea Who Refuse Continuous Positive Airway Pressure Treatment

A Randomized Trial

Table 1. Demography and Characteristics at Baseline

Parameter	Pitolisant (*n* = *201*)	Placebo (*n* = *67*)	All Patients (*N* = *268*)
Age, yr, mean (SD) (range)	51.9 (10.6) (25–75)	52.1 (11.0) (30–76)	52.0 (10.6) (25–76)
Sex, *n* (%)			
M	151 (75.1)	51 (76.1)	202 (75.4)
F	50 (24.9)	16 (23.9)	66 (24.6)
Weight at inclusion, kg, mean (SD)	97.7 (15.7)	99.8 (16.1)	—
BMI, kg/m^2, mean (SD)	32.8 (4.6)	33.0 (4.3)	—
Cardiovascular disease, *n* (%)	110 (54.7)	35 (52.2)	145 (54.1)
AHI at date of diagnosis, events/h, mean (SD)	50.2 (44.3)	46.9 (22.8)	49.3 (40.0)
Nocturnal Sa_{O_2} at date of diagnosis, %, mean (SD)	89.8 (9.1)	90.9 (3.8)	90.1 (8.2)

Definition of abbreviations: AHI = apnea–hypopnea index; BMI = body mass index.

Am J Respir Crit Care Med 2020; 201: 1135–1145.

Pitolisant for Daytime Sleepiness in Patients with Obstructive Sleep Apnea Who Refuse Continuous Positive Airway Pressure Treatment

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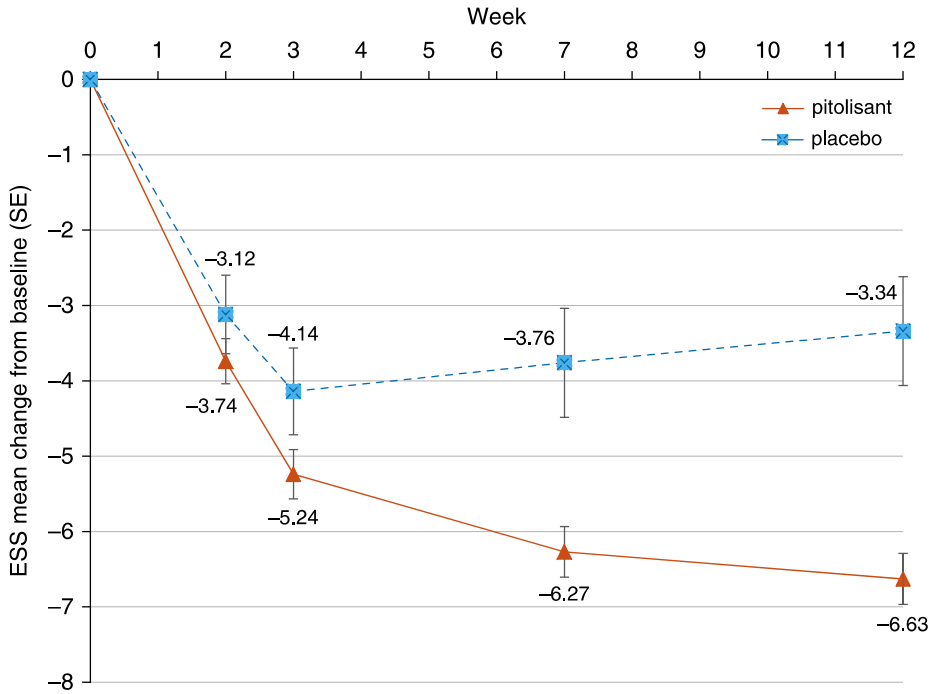

Figure 3. Changes in Epworth Sleepiness Scale (ESS) score during treatment.

Am J Respir Crit Care Med 2020; 201: 1135–1145.

Pitolisant for Daytime Sleepiness in Patients with Obstructive Sleep Apnea Who Refuse Continuous Positive Airway Pressure Treatment

A Randomized Trial

Table 2. Efficacy Results for Primary Endpoint: ESS Score

Parameter	Pitolisant (*n* = *201*)	Placebo (*n* = *67*)	*P* Value
ESS score at inclusion, mean (SD)	15.7 (3.1)	15.7 (3.6)	—
ESS score at end of treatment, mean (SD)	9.1 (4.7)	12.2 (6.1)	—
Final ESS score, DB-LOCF, mean (SD) (95% CI)	9.4 (4.6) (8.8–10.1)	12.1 (5.8) (10.7–13.5)	<0.001
ESS score change, DB-LOCF − V2	−6.3 (4.5)	−3.6 (5.5)	<0.001
R_1 response (ESS score ⩽10)			
n (%)	135 (67.2)	30 (44.8)	<0.001
95% CI	60.2–73.6	32.6–57.4	
R_2 response (ESS score ⩽10 or ESS score improvement ⩾3)			
n (%)	162 (80.6)	36 (53.7)	<0.001
95% CI	74.4–85.8	41.1–66.0	

Definition of abbreviations: CI = confidence interval; DB-LOCF = database with last observation carried forward; ESS = Epworth Sleepiness Scale; R_1 = first secondary enpoint result; R_2 = second secondary endpoint result; V2 = visit 2.

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Pitolisant for Daytime Sleepiness in Patients with Obstructive Sleep Apnea Who Refuse Continuous Positive Airway Pressure Treatment

A Randomized Trial

Table 3. Efficacy Results for Secondary Outcomes

Parameter	Pitolisant ($n = 201$)	Placebo ($n = 67$)	*P* Value
OSLER test			
OSLER test mean sleep latency at inclusion, min, (SD)	14.79 (10.95)	15.92 (11.04)	—
Number of patients with OSLER test = 40 min at inclusion	11 (5.5%)	4 (6%)	—
Number of patients with OSLER test ⩾30 min and <40 min at inclusion	13 (6.5%)	3 (4.5%)	—
OSLER test mean sleep latency at end of treatment, min	21.95 (13.53)	20.25 (13.42)	—
Ratio of OSLER test V6/OSLER test V2, geometric mean	1.65	1.39	0.120
Mean difference of pitolisant and placebo logarithms of sleep latency at end of DB treatment (95% CI)	0.1 (0.0–0.3)		—
Normal vigilance (number of 3–6 and ⩾7 errors = 0 for each of the three tests)			
At baseline (V2)	2.0% (0.5–5.0%)	3.0% (0.4–10.4%)	—
At the end of DB treatment (V6)	8.5% (4.9–13.5%)	6.3% (1.7–15.2%)	0.487
Pichot fatigue score, mean change (SD)	−3.6 (5.6)	−1.0 (6.3)	0.005
Sleep diary variables			
Mean change in daily number of sleep/sleepiness episodes (SD)	−1.79 (1.97)	−1.30 (1.86)	0.056*
Mean change in daily duration of sleep/sleepiness episodes (SD)	−47.87 (53.39)	−32.24 (48.82)	0.066†
EQ-5D, mean change in VAS score	7.3 ± 16.2	1.8 ± 16.3	0.059
Leeds Sleep Evaluation Questionnaire			
Mean change in modified getting to sleep (SD)	10.21 (24.99)	2.42 (23.51)	0.155
Mean change in quality of sleep (SD)	17.70 (26.08)	13.00 (25.56)	0.108
Mean change in awake after sleep (SD)	19.19 (26.61)	14.00 (25.18)	0.160
Mean change in behavior after awakening (SD)	21.96 (22.26)	13.35 (20.89)	0.018
Mean change in global LSEQ score (SD)	17.26 (14.80)	10.69 (14.80)	0.005
TMT A, mean change in average time (SD)	−8.9 (12.7)	−7.3 (13.7)	0.389
TMT B, mean change in average time (SD)	−22.5 (40.0)	−16.3 (33.8)	0.648
CGI			<0.001
Very much improved	21 (11.1%)	3 (4.7%)	
Much improved	84 (44.2%)	19 (29.7%)	
Minimally improved	55 (28.9%)	14 (21.9%)	
No change	30 (15.8%)	22 (34.4%)	
Minimally worse	0 (0.0%)	6 (9.4%)	
Much worse	0 (0.0%)	0 (0.0%)	
Very much worse	0 (0.0%)	0 (0.0%)	
CGI improvement at end of DB treatment (V6)			
n (%)	160 (84.2%)	36 (56.3%)	
95% CI	78.2–89.1%	43.3–68.6%	
Patient's global opinion			<0.001
Improvement at V6, *n* (%)	164 (86.3%)	39 (60.9%)	
95% CI	80.6–90.9%	47.9–72.9%	

Definition of abbreviations: CGI = Clinical Global Impression; CI = confidence interval; DB = double-blind; EQ-5D = EuroQol five-dimension quality of life scale; LSEQ = Leeds Sleep Evaluation Questionnaire; OSLER = Oxford Sleep Resistance test; TMT = Trail Making Test; V2 = visit 2; V6 = visit 6; VAS = visual analogue scale.

*$P = 0.049$ in the per-protocol population.

†$P = 0.050$ in the per-protocol population.

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Efficacy of Pitolisant 20 mg in Reducing Excessive Daytime Sleepiness and Fatigue in Patients with Obstructive Sleep Apnoea Syndrome: An Individual Patient Data Meta-analysis

Philippe Lehert[1,2]

Table 1 Comparison of baseline characteristics between treatment groups in the HAROSA-1 and HAROSA-2 studies

Baseline characteristics	HAROSA-1 (with CPAP)		HAROSA-2 (without CPAP)	
	Pitolisant	Placebo	Pitolisant	Placebo
Participants, *n*	183	61	201	67
Gender, male: *n* (%)	149 (81.4)	53 (86.9)	151 (75.1)	51 (76.1)
In employment *n* (%)	117 (63.9)	50 (82.0)	139 (69.2)	49 (73.1)
Age (years)	53.77 ± 10.5	50.95 ± 10.6	51.94 ± 10.6	52.12 ± 11.0
Baseline ESS (scale unit)	14.9 ± 2.7	14.6 ± 2.8	15.7 ± 3.1	15.7 ± 3.6
Baseline OSleR (minutes)	20.2 ± 11.9	23.3 ± 12.1	14.8 ± 10.9	15.9 ± 11.0
ESS and OSleR *Z*-score (*Z*-unit)	0.07 ± 0.64	0.22 ± 0.64	− 0.28 ± 0.79	− 0.22 ± 0.86
Pichot Fatigue scale (scale unit)	13.2 ± 7.2	11.4 ± 7.2	13.0 ± 6.5	11.1 ± 5.9

Mean ± SD values, unless specified otherwise

CPAP continuous positive airway pressure, *ESS* Epworth Sleepiness Scale, *OSleR* Oxford Sleep Resistance test

Efficacy of Pitolisant 20 mg in Reducing Excessive Daytime Sleepiness and Fatigue in Patients with Obstructive Sleep Apnoea Syndrome: An Individual Patient Data Meta-analysis

Philippe Lehert[1,2]

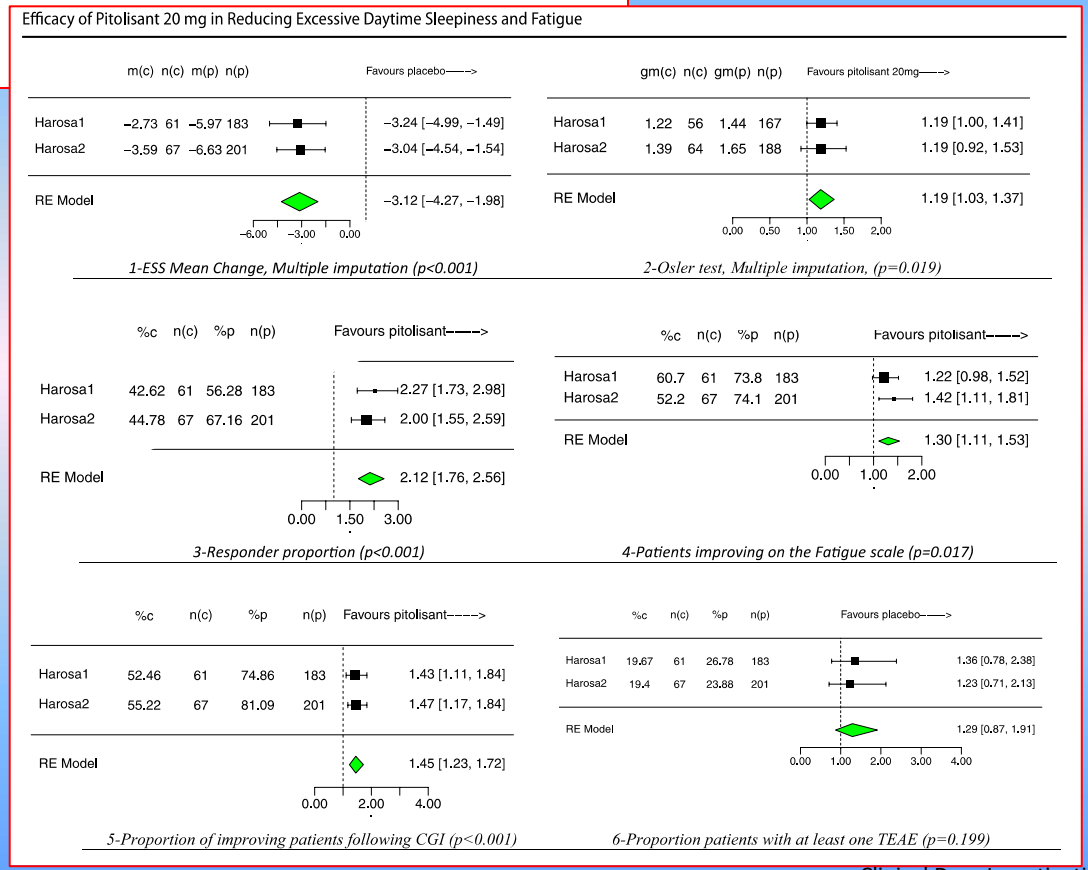
Table 2 Summary of results

Endpoints	Placebo[a]	Pitolisant[a]	IPD Test[b]	Summary means[c]
ESS (scale unit)	− 3.2	− 5.9	− 3.1 (− 4.1; − 2.1), < 0.001	− 3.1 (− 4.3; − 2), < 0.001
OSleR (min)	1.3	1.6	1.18 (1.02; 1.35), 0.022	1.19 (1.03; 1.37), 0.019
EDS *Z*-score (*Z*-unit)	0.77	1.54	0.71 (0.46; 0.97), < 0.001	0.74 (0.46; 1.01), < 0.001
Improving patients on CGI (%)	54.9%	78.1	1.46 (1.12;1.89), < 0.001	1.45 (1.23; 1.72), < 0.001
Therapy responder (%)	32.0%	56.2%	1.76 (1.39; 2.24), < 0.001	1.72 (1.36; 2.17), < 0.001
Pichot Fatigue Scale (scale unit)	− 1.9	− 3.7	− 1.3 (− 2.3; − 0.2), 0.017	− 1.65 (3.21; − 0.10), 0.037
Patients improving fatigue (%)	56.2%	74.0%	1.3 (1.11, 1.53), 0.001	1.3 (1.11, 1.53), 0.001

Clinical Drug Investigation, 2021

Efficacy of Pitolisant 20 mg in Reducing Excessive Daytime Sleepiness and Fatigue in Patients with Obstructive Sleep Apnoea Syndrome: An Individual Patient Data Meta-analysis

Philippe Lehert[1,2]



Clinical Drug Investigation, 2021

Efficacy of Pitolisant 20 mg in Reducing Excessive Daytime Sleepiness and Fatigue in Patients with Obstructive Sleep Apnoea Syndrome: An Individual Patient Data Meta-analysis

Philippe Lehert[1,2]

Table 3 TEAE occurrence observed with more than 2% in one of the two arms for the two studies

TEAE	Placebo (n = 128)	Pitolisant (n = 383)	p value
Nausea/diarrhoea	10	32	0.991
Infections	8	29	0.763
Insomnia	4	28	0.138
Headache	15	44	0.993

TEAE treatment-emergent adverse events

Clinical Drug Investigation, 2021

Conclusion

- Après 12 semaines de traitement, le Pitolisant (5-20mg/jour) améliore la somnolence diurne résiduelle chez les SAOS modérés à sévères, appareillés par PPC et observants et les patients non traités par PPC
- Amléioration de la SDE améliore la vigilance, les fonction cognitives, la performance au travail
- Sans recul sur l'efficacité et la sécurité à long terme (essai sur 9 mois en cours)
- Sans avoir l'ambition de se substituer à la PPC

HAS
HAUTE AUTORITÉ DE SANTÉ

OZAWADE (pitolisant)

AVIS SUR LES MÉDICAMENTS - Mis en ligne le 10 févr. 2022

Nature de la demande

Inscription

Première évaluation

Avis favorable au remboursement uniquement pour améliorer l'éveil et réduire la somnolence diurne excessive (SDE) chez les patients présentant un SAHOS modéré à sévère et étant :

- soit observants à un traitement primaire du SAHOS tel que la pression positive continue (PPC) et dont la somnolence n'a pas été traitée de façon satisfaisante
- soit intolérants à ce traitement.

Avis défavorable au remboursement dans les autres situations cliniques de l'AMM.

Service Médical Rendu (SMR)

Important	Le service médical rendu par OZAWADE (pitolisant) est : • important pour améliorer l'éveil et réduire la somnolence diurne excessive (SDE) chez les patients présentant un SAHOS modéré à sévère et étant : – soit observants à un traitement primaire du SAHOS tel que la pression positive continue (PPC) et dont la somnolence n'a pas été traitée de façon satisfaisante, – soit intolérants à ce traitement.
Insuffisant	Le service médical rendu par OZAWADE (pitolisant) est insuffisant pour justifier d'une prise en charge par la solidarité nationale dans les autres situations cliniques de l'AMM correspondant : • soit aux patients présentant un SAHOS léger, • soit aux patients présentant un SAHOS modéré à sévère et étant non observants à un traitement primaire du SAHOS tel que la pression positive continue (PPC) avec somnolence persistante.

Amélioration du service médical rendu (ASMR)

IV (mineur)	La Commission considère que OZAWADE (pitolisant) apporte : • une amélioration du service médical rendu mineure (ASMR IV) au même titre que SUNOSI (solriamfetol) dans la stratégie thérapeutique actuelle pour améliorer l'éveil et réduire la somnolence diurne excessive (SDE) chez les patients observants à un traitement primaire du SAHOS tel que la pression positive continue (PPC), et dont la somnolence n'a pas été traitée de façon satisfaisante. • une amélioration du service médical rendu mineure (ASMR IV) dans la stratégie thérapeutique actuelle pour améliorer l'éveil et réduire la somnolence diurne excessive (SDE) chez les patients intolérants à un traitement primaire du SAHOS.