Therapeutic Class Review
Narcolepsy Agents

MEDICATION*	MARKETER	AVAILABILITY
Nuvigil (armodafinil)	Teva Pharmaceuticals	**Brand/Generic:** 50, 150, 200, 250 mg tablets
Provigil (modafinil)	Teva Pharmaceuticals	**Brand/Generic:** 100, 200 mg tablets
Sunosi (solriamfetol)	Jazz Pharmaceuticals	**Brand:** 75, 150 mg tablets
Wakix (pitolisant)	Harmony Biosciences, LLC	**Brand:** 4.45, 17.8 mg tablets
Xyrem (sodium oxybate)	Jazz Pharmaceuticals	**Brand:** 500 mg/mL oral solution
Xywav (calcium, magnesium, potassium, and sodium oxybates)	Jazz Pharmaceuticals	**Brand:** 500 mg/mL oral solution

Therapeutic Classes:
- Central Nervous System (CNS) Stimulants (armodafinil, modafinil)
- Histamine-3 (H_3) Receptor Antagonist/Inverse Agonist (pitolisant)
- CNS Depressants (sodium oxybate/oxybate salts)
- Dopamine and Norepinephrine Reuptake Inhibitor (DNRI) (solriamfetol)

Purpose of Review: To evaluate the safety and efficacy of agents used for narcolepsy, including the new formulation, Xywav (oxybate salts), for formulary consideration.

* Brand names are indicated by bolded text; generic-only products are indicated by non-bolded text

Note: Information on indications, pharmacology, dosing, and safety has been obtained from the prescribing information for the individual products, except where noted otherwise.

SUMMARY

Background

- Narcolepsy is a chronic neurological disorder of hypersomnia and its associated symptoms are potentially debilitating. Narcolepsy is typically classified as type 1 (narcolepsy with cataplexy) or type 2 (narcolepsy without cataplexy) (*Bhattarai & Sumerall 2017, Szabo et al 2019*). Narcolepsy type 1 is estimated to have a prevalence of 25 to 50 per 100,000 people. Narcolepsy typically begins in the teens and early twenties, but occasionally occurs as early as age 5 or after age 40. The prevalence of narcolepsy type 2 is uncertain, as it is less well studied and more difficult to diagnose; however, it has been estimated as 20 to 34 per 100,000 people (*Scammel 2020a*). Excessive daytime sleepiness (EDS) is present in all patients with narcolepsy. Other symptoms include cataplexy, hypnagogic hallucinations, and sleep paralysis; however, only about one-third of patients have all 4 symptoms (*Scammell 2020a*). Patients may also experience fragmented nighttime sleep. Patients with narcolepsy have been shown to be at increased risk for cardiovascular (CV), metabolic, and psychiatric comorbidities compared with individuals without narcolepsy (*Xywav dossier 2020*). Pharmacological interventions are the most common approach for treating narcolepsy. Current medications have been developed to target symptoms; however, most patients do not experience complete resolution despite receiving optimal standard treatment (*Bhattarai & Sumerall 2017, Scammell 2020b).*
- Obstructive sleep apnea (OSA) is a disorder that is characterized by obstructive apneas and hypopneas caused by repetitive collapse of the upper airway during sleep. The diagnosis should be considered whenever a patient presents with symptoms such as EDS, snoring, and choking or gasping during sleep, particularly in the presence of risk factors such as obesity, male gender, and advanced age (*Kline 2019*). Besides EDS, untreated OSA has many potential adverse clinical consequences including impaired daytime function, metabolic dysfunction, and an increased risk of CV disease and mortality. All patients diagnosed with OSA should be offered positive airway pressure (PAP) as initial therapy. Continuous positive airway pressure (CPAP) involves maintenance of a positive pharyngeal transmural pressure so that the intraluminal pressure exceeds the surrounding pressure. CPAP also stabilizes the upper airway through increased end expiratory lung volume. As a result, respiratory events due to upper airway collapse (eg, apneas, hypopneas) are prevented. Other options to PAP include oral appliances or upper airway surgery in severe cases with a surgically correctable upper airway obstruction. Wakefulness-promoting pharmacological agents (eg,

modafinil, armodafinil) may be beneficial as adjunctive therapy for EDS that persists despite adequate and successful conventional OSA therapy (*Kryger 2020*).

- Shift work disorder (SWD) is a circadian rhythm sleep disorder that occurs in individuals who work night shifts. These individuals commonly experience difficulties with both sleep and alertness at desired times, and shift work is increasingly recognized as a risk factor for a variety of adverse health outcomes, including diabetes, cancer, and CV disease. While some shift workers show circadian adjustment to their work schedule, most do not. Up to one-third of shift workers report regular, persistent complaints of insomnia and/or excessive sleepiness that meet formal criteria for SWD (ie, development of sleep disturbances and impairment of waking alertness and performance) (*Cheng & Drake 2019, Morgenthaler et al 2007b*). Minimum measures to improve sleep after a night shift include a regular sleep schedule (ie, "anchor sleep"), light-blocking shades, and ambient noise control. Treatment with modafinil or armodafinil is an option in patients with persistent sleepiness in conjunction with nonpharmacologic measures to improve sleep and alertness. The magnitude of benefit may vary among individuals. The observed benefits in randomized controlled trials (RCTs) have been modest, however, and adverse effects (AEs) may outweigh benefits in some patients (*Cheng & Drake 2019*).

Indications

- Provigil/Nuvigil
  - Provigil (modafinil) received Food and Drug Administration (FDA) approval to improve wakefulness in adult patients with excessive sleepiness associated with narcolepsy in December 1998; approval was granted for OSA and SWD in January 2004 (*FDA Web site*).
  - Nuvigil (armodafinil), the R-enantiomer of modafinil, was approved as a new formulation in June 2007 to improve wakefulness in adult patients with excessive sleepiness associated with narcolepsy, OSA, or SWD (*FDA Web site*).
  - Modafinil and armodafinil are both Schedule IV controlled substances.
- Sunosi (solriamfetol), received FDA approval in March 2019 to improve wakefulness in adult patients with EDS associated with narcolepsy or OSA (*FDA Web site*). Solriamfetol has orphan drug designation in the U.S. for narcolepsy (*Sunosi press release 2019*). Solriamfetol is a Schedule IV controlled substance.
- Wakix (pitolisant), received FDA approval on August 15, 2019 for the treatment of EDS in adults with narcolepsy with orphan and priority review designations. In October 2020, pitolisant gained approval for the additional indication of cataplexy in adults. Pitolisant has shown no abuse potential and is the only unscheduled agent indicated for the treatment of narcolepsy and narcolepsy-cataplexy (*FDA web site*).
- Xyrem/Xywav
  - Xyrem (sodium oxybate) was approved in July 2002 with orphan drug status under priority review for the treatment of cataplexy associated with narcolepsy. Use of Xyrem was expanded to the pediatric population in October 2018 (*FDA Web site*). Xyrem is indicated for the treatment of cataplexy or EDS in patients 7 years of age and older with narcolepsy. A new formulation of oxybate salts, Xywav, received FDA approval in July 2020 for the same indication as Xyrem (*FDA Web site, Xywav dossier 2020*). Xywav contains the same active moiety as Xyrem but is made up of a unique composition of cations (calcium, magnesium, potassium, and sodium oxybates) that contains 92% less sodium than Xyrem at all nightly doses. Xyrem and Xywav are Schedule III controlled substances (*Xywav dossier 2020*).
    - The recommended daily adult dose of Xyrem (6 to 9 g/night) adds 1100 to 1640 mg of sodium to total daily intake, which accounts for 73 to 109% of the total daily sodium intake (no more than 2300 mg and ideally < 1500 mg for most adults) recommended by the American Heart Association (AHA) (*AHA 2017*). The Xyrem product labeling includes a warning regarding the high sodium content and advises monitoring of symptoms and daily sodium intake in patients sensitive to salt intake (eg, those with heart failure [HF], hypertension [HTN], or renal impairment) (*Xyrem prescribing information 2020*).

Pharmacology

- The mechanism(s) through which modafinil/armodafinil promotes wakefulness is unknown, but may involve increased dopaminergic signaling through blocking of dopamine reuptake in a manner distinct from amphetamines (*Scammell 2020a*).
  - PK studies have shown that R-modafinil has a longer half-life than S-modafinil (10 to 14 vs 3 to 4 hours). Additionally, it has been reported that the elimination of S-modafinil is 3 times faster than that of R-modafinil. Because R-modafinil has a longer half-life than modafinil, its administration results in higher plasma concentrations later in the waking day compared with modafinil on a ''mg-to-mg'' basis (*Harsh et al 2006*).
- The mechanism of action of pitolisant in EDS in adult patients with narcolepsy is unclear. However, its efficacy could be mediated through its activity as an antagonist/inverse agonist at histamine-3 (H_3) receptors.
- Sodium oxybate is a central nervous system (CNS) depressant. Its mechanism of action in the treatment of narcolepsy is unknown. Xyrem (sodium oxybate) is the sodium salt of gamma-hydroxybutyrate (GHB), an endogenous compound

and metabolite of the neurotransmitter gamma-aminobutyric acid (GABA). Oxybate salts is a mixture of calcium oxybate, magnesium oxybate, potassium oxybate, and sodium oxybate. It is hypothesized that the therapeutic effects of sodium oxybate and oxybate salts on cataplexy and EDS are mediated through GABA actions at noradrenergic and dopaminergic neurons, as well as at thalamocortical neurons (*Xywav prescribing information 2020*).

- Solriamfetol is a selective dopamine and norepinephrine reuptake inhibitor (DNRI) with wake-promoting effects (*Scammell 2020a*).

Clinical Efficacy

- Efficacy measures
  - Objective measures of EDS as assessed by sleep latency (ie, the time interval between attempting to fall asleep and the onset of sleep) measured using polysomnography (PSG):
    - Maintenance of Wakefulness Test (MWT) (*Freedman 2019*)
      - The MWT measures an individual's ability to remain awake during the daytime in a darkened, quiet environment. Patients are instructed to remain awake for as long as possible during serial 40-minute test sessions, and sleep latency is determined as the mean number of minutes patients could remain awake in the first 4 test sessions. Among healthy individuals, the mean sleep latency is approximately 30 minutes, with > 97% of individuals having a mean sleep latency ≥ 8 minutes; thus, a mean sleep latency < 8 minutes is generally considered abnormal. Staying awake for at least 40 minutes during all 4 sessions is strong objective evidence that an individual can stay awake. A mean sleep latency between 8 and 40 minutes has uncertain significance.
    - Multiple Sleep Latency Test (MSLT) (*American Sleep Association Web site, Thorpy 1992*)
      - The MSLT also measures an individual's ability to remain awake during the daytime in ideal quiet conditions. The MSLT consists of 5 nap opportunities to determine both severity of sleepiness and presence of 2 or more sleep onset rapid eye movement (REM) periods. The absence of sleep on any nap opportunity is recorded as a sleep latency of 20 minutes. A mean sleep latency of 0 to 5 minutes indicates severe sleepiness, while 5 to 10 minutes is rated as moderate sleepiness.
  - Subjective measures of EDS:
    - Epworth Sleepiness Scale (ESS) (*Johns 1991*)
      - The ESS is an 8-item questionnaire by which patients rate their perceived likelihood of falling asleep during usual daily life activities.
      - The score ranges from 1 to 24 points; 9 to 24 points indicates abnormal (possibly pathologic) sleepiness.
    - Clinical Global Impression of Change (CGI-C)
      - The CGI-C is a 7-point physician-rated scale that assesses symptom severity and treatment response (range: 1 [very much improved] to 7 [very much worse]).
    - Patient Global Impression of Change (PGI-C)
      - The PGI-C is a 7-point patient-rated scale that assesses their symptom change from baseline (range: 1 [very much improved] to 7 [very much worse]).
  - Sustained Attention to Response Task (SART) (*Fronczek et al 2006*)
    - The SART is an objective laboratory measure of sustained vigilance and attention. Patients are presented with a series of numbers (ranging from 1 to 9) 225 times. Patients must press a button except when the number presented is 3. The SART comprises 3 error scores: the number of times a button was pressed inappropriately ("NO GO"), the number of times key pressing was missed ("GO"), and the sum of these 2 scores.
- Modafinil/armodafinil:
  - A systematic review and meta-analysis (9 RCTs, N = 1054) was conducted to evaluate the efficacy and safety of modafinil (any dose or regimen) vs no active treatment or other drugs in the treatment of narcolepsy (*Golicki et al 2010*). The primary endpoints were elimination of EDS assessed by objective laboratory tests (MSLT, MWT) or validated subjective outcome measures (ESS) and number and duration of severe somnolence, sleep attacks and naps, as reported by patients.
    - Compared with placebo, modafinil significantly increased mean sleep latency assessed by the MSLT (3 studies): weighted mean difference (WMD) 1.11 minutes (95% confidence interval [CI], 0.55 to 1.66); I^2 = 0%; test for overall effect: Z = 3.90 (p < 0.0001). As assessed by the MWT (6 studies), there was a greater increase in mean sleep latency with modafinil vs placebo: WMD 2.82 minutes (95% CI, 2.40 to 3.24); I^2 = 0%; test for overall effect: Z = 13.14 (p < 0.00001). Compared with placebo, modafinil significantly reduced the ESS score (6 studies): WMD -2.73 points (95% CI, -3.39 to -2.08); I^2 = 0%; test for overall effect: Z = 8.17 (p < 0.00001). Modafinil also improved the number (p = 0.006) and duration (p = 0.03) of severe somnolence episodes, sleep attacks, and naps per day as compared with placebo, but did not reduce the number of cataplexy attacks per day (4 studies): WMD 0.02 (95% CI, -0.27 to 0.31); I^2 = 71%; test for overall effect: Z = 0.13 (p = 0.90). Quality of life (QoL) as measured by the Short Form (SF)-36 and validated narcolepsy-specific questionnaire (2 studies) indicated

significant improvement with modafinil vs placebo in 5 out of 7 narcolepsy-specific domains, SF-36 mental health summary scale and 4 (modafinil 200 mg/day) or 5 (modafinil 400 mg/day) SF-36 domains.

- A 12-week, Phase 3, double-blind (DB), placebo-controlled (PC), multicenter (MC) RCT (N = 196) assessed the efficacy and safety of armodafinil for the treatment of EDS in patients with narcolepsy (*Harsh et al 2006*). Patients were randomized to either armodafinil 150 or 250 mg once daily. The co-primary endpoints were change from baseline in mean sleep latency on the MWT 9:00 AM to 3:00 PM and the proportion of patients with at least minimal improvement on the physician-rated CGI-C.
  - At the final visit, mean MWT 9:00 AM to 3:00 PM sleep latency increased 1.3, 2.6, and 1.9 minutes from baseline in the 150 mg, 250 mg, and armodafinil combined groups, respectively, and decreased 1.9 minutes from baseline in the placebo group. Treatment differences from placebo were 3.2, 4.5, and 3.8 minutes in the 150 mg, 250 mg, and armodafinil combined groups, respectively (all $p < 0.01$). The proportion of patients with at least minimal improvement in the CGI-C was significantly higher for the armodafinil 150 mg, 250 mg, and combined groups compared with placebo at all time points during the study ($p < 0.0001$ for both individual doses and the combined group vs placebo at final visit). The proportion of patients rated as minimally, much, and very much improved on the CGI-C from baseline to final visit was 21%, 33% and 16%, respectively, for armodafinil 150 mg; 20%, 35%, and 18%, respectively, for armodafinil 250 mg; 20%, 34%, and 17%, respectively, for the armodafinil combined group; and 17%, 12%, and 3%, respectively, for placebo. Armodafinil 150 and 250 mg/day reduced the mean daily number of unintended sleep episodes by 33% and 44%, respectively, compared with a 10% reduction in the placebo group ($p < 0.0001$ for overall treatment comparison). The mean number of daily naps was reduced by 41%, 44%, and 22%, respectively, for the armodafinil 150 mg, armodafinil 250 mg, and placebo groups ($p = 0.0039$ for overall treatment comparison). The mean number of mistakes/near misses/accidents was reduced by 43% and 30% in the armodafinil 150 mg and 250 mg groups, respectively, compared with a 10% reduction in the placebo group; however, these differences were not statistically significant ($p = 0.1792$ for overall treatment comparison).
- A systematic review and meta-analysis (11 modafinil RCTs [N = 723] and 5 armodafinil RCTs [N = 1009]) evaluated the efficacy of modafinil and armodafinil in treating EDS in patients with OSA (*Kuan et al 2016*). Most trials investigated whether modafinil or armodafinil with concurrent CPAP use improved sleepiness, neurocognitive performance, and functional outcome in patients with sleep apnea. The primary endpoints were sleep latency assessed by the MSLT or MWT, ESS, Karolinska Sleepiness Scale (KSS), and Stanford Sleepiness Scale (SSS).
  - ESS scores in patients receiving CPAP were significantly reduced with modafinil (5 RCTs, WMD, -2.95 [95% CI, -3.73 to -2.17]) and armodafinil (4 RCTs, WMD, -2.78 [95% CI, -3.51 to -2.05]) compared with placebo ($I^2 = 0\%$). Sleep latency assessed by the MWT was significantly increased in the modafinil group (WMD, 2.51 [95% CI, 1.5 to 3.52]) and in the armodafinil group (WMD, 2.71 [95% CI, 0.02 to 5.37]) vs placebo. However, a meta-analysis of data from 3 RCTs that compared the effects of modafinil and placebo on sleep latency, as assessed by the MSLT found no significant differences. Four studies evaluated the effects of modafinil on subjective sleepiness during acute CPAP withdrawal or in CPAP-naïve patients with OSA. There was a significant reduction in daytime sleepiness duration ($p < 0.05$), significant improvements on the ESS ($p = 0.003$), KSS ($p = 0.04$ and $p = 0.01$), SSS ($p = 0.03$), and daytime sleepiness visual analog scale ($p = 0.01$). A non-significant trend of improved self-reported sleepiness on the ESS after armodafinil use among patients with OSA before CPAP treatment was observed in 1 study ($p = 0.066$). The proportion of patients with improvement on the CGI-C was evaluated in 3 RCTs of modafinil and 4 RCTs of armodafinil. There was significant improvement in both the modafinil and armodafinil groups vs the placebo group, with pooled risk ratios (RR) of 1.94 (95% CI, 1.53 to 2.44) and 1.48 (95 % CI, 1.17 to 1.87), respectively. The results on neurocognitive performance were inconsistent.
- A 3-month, Phase 3, DB, PC, MC RCT (N = 209) investigated the efficacy and safety of modafinil for the treatment of sleepiness in patients with SWD (*Czeisler et al 2005*). Patients received modafinil 200 mg 30 to 60 minutes before each night shift. The primary endpoints were the CGI-C rating for sleepiness during the night shift, including the commute to and from work, at the final visit and change between baseline and the final visit in overall mean sleep latency based on nighttime MSLT.
  - Seventy-four percent of patients in the modafinil group were rated as at least minimally improved on the CGI-C at the final visit, as compared with 36% in the placebo group ($p < 0.001$). Overall mean sleep latency, as measured by the MSLT, increased from 2.1 minutes at baseline to 3.8 minutes at the final visit with modafinil (change, 1.7 minutes; $p < 0.001$) but not with placebo (2.04 at baseline vs 2.37 at the final visit; change, 0.3; $p = 0.24$). Sleep latency was significantly greater in the modafinil group than in the placebo group ($p = 0.002$). This improvement in sleep latency with modafinil vs placebo was found at 2:00 AM ($p = 0.02$) and 4:00 AM ($p < 0.001$), but not at 6:00 AM ($p = 0.45$) or 8:00 AM ($p = 0.17$). Patients who were receiving modafinil also had a reduction in the frequency and duration of lapses of attention during nighttime testing of their performance on the Psychomotor Vigilance Test (change from baseline, a reduction in lapse frequency of 2.6 vs an increase of 3.8, respectively; $p < 0.001$), and fewer proportions of patients reported having had accidents or near accidents while commuting home (29%

vs 54%, respectively; < 0.001). Despite these benefits, patients treated with modafinil continued to have excessive sleepiness and impaired performance at night.

- A 12-week, DB, PC, MC RCT (N = 254) assessed the effect of armodafinil on the physiologic propensity for sleep and cognitive performance during usual night shift hours in patients with excessive sleepiness associated with chronic moderate to severe SWD (*Czeisler et al 2009*). The primary endpoints were change from baseline to final visit in overall mean sleep latency as assessed by the MSLT and the proportion of patients with at least minimal improvement in the CGI-C during the night shift and commute to and from work at the final visit.
  - Armodafinil significantly improved mean sleep latency from 2.3 minutes at baseline to 5.3 minutes at final visit, compared with a change from 2.4 minutes to 2.8 minutes in the placebo group (p < 0.001). A total of 89 (79%) armodafinil patients were rated as improved on the CGI-C at the final visit compared with 61 (59%) of the placebo patients (p = 0.001). At the final visit, armodafinil was associated with significant improvement as reported in patient diaries, including maximum level of sleepiness during the night shift (p < 0.001) and commute home (p = 0.003) and the mean number of mistakes, accidents, or near misses during the night shift (p = 0.004), but not during the commute home (p = 0.12) compared with placebo.
- A 40-week, open-label (OL) extension study assessed the long-term efficacy and safety of modafinil in 478 patients with EDS associated with narcolepsy who completed 1 of the 2 pivotal 9-week RCTs of modafinil (*Mitler et al 2000*). A flexible-dose regimen (ie, 200, 300, or 400 mg daily) was followed in 1 study. In the second study, patients received 200 mg/day for 1 week, followed by 400 mg/day for 1 week, then either 200 or 400 mg doses for the duration of the study; the majority (~75%) received 400 mg/day.
  - Disease severity improved in > 80% of patients throughout the 40-week study. At weeks 2, 8, 24, and 40, disease severity was “much improved” or “very much improved” in 49, 58, 59, and 58% of patients, respectively. The mean ESS score improved significantly from 16.5 at OL baseline to 12.4 at week 2 and remained at that level through week 40 (p < 0.001). QoL scores at weeks 4, 8, 24, and 40 were significantly improved vs OL baseline scores for 6 of the 8 SF-36 domains (p < 0.001). The most common treatment-related AEs were headache (13%), nervousness (8%), and nausea (5%). Most AEs were mild to moderate. Forty-three patients (9.0%) discontinued treatment because of AEs.
- The long-term efficacy and safety of armodafinil in patients with EDS associated with treated OSA, SWD, or narcolepsy who completed one of four 12-week pivotal RCTs were assessed in a 12-month, flexible-dose (50 to 250 mg/day), OL extension study. Of 743 enrolled patients (474 with treated OSA, 113 with SWD, and 156 with narcolepsy), 57% of patients completed 12 months or more of treatment (*Black et al 2010*).
  - Compared with baseline, minimal or greater improvement on the CGI-C was reported by most patients in the 3 diagnostic groups (75% to 92%) at final visit; patients in the SWD group reported the greatest improvement. A rating of much or very much improved was reported at the final visit by 65% (295/457) of patients with treated OSA (95% CI, 60.2 to 68.9), 88% (92/105) with SWD (95% CI, 81.3 to 93.9), and 62% (93/150) with narcolepsy (95% CI, 54.2 to 69.8). At baseline, the proportion of patients with a normal ESS score (ie, < 10) was 0.4% (2/454) in the treated OSA group and 3.4% (5/147) in the narcolepsy group. At the final visit, the mean ESS score was reduced by 6.4 (95% CI, -6.90 to -5.94) in the treated OSA group and by 4.3 (95% CI, -5.20 to -3.49) in the narcolepsy group. The proportion of patients with an ESS score < 10 at final visit was 54.8% (249/454) for treated OSA and 31.3% (46/147) for narcolepsy. At final visit, mean global Brief Fatigue Inventory (BFI) scores were reduced by 1.7 (95% CI, -1.88 to -1.43) in the treated OSA group, 2.3 (95% CI, -2.75 to -1.87) in the SWD group, and 1.7 (95% CI, -2.13 to -1.35) in the narcolepsy group; mean worst fatigue scores were reduced by 1.8 (95% CI, -2.13 to -1.57) in the treated OSA group, 2.4 (95% CI, -3.06 to -1.83) in the SWD group, and 1.5 (95% CI, -2.00 to -1.07) in the narcolepsy group. The most commonly reported AEs were headache (25%), nasopharyngitis (17%), insomnia (14%), and upper respiratory tract infection (10%). Most AEs were mild or moderate.

- Pitolisant:
  - The efficacy and safety of pitolisant were evaluated in two Phase 3, active-controlled, DB, PC, MC pivotal RCTs conducted in Europe/South America evaluating the treatment of EDS in adults with narcolepsy with or without cataplexy (HARMONY 1 and HARMONY 1bis) (*Dauvilliers et al 2013*, *Wakix dossier 2019, Wakix FDA clinical review 2019*). Both studies included an 8-week treatment period which consisted of a 3-week dose titration phase followed by a 5-week stable dose phase. During the 3-week flexible dosing period, the dose was determined according to the investigator’s judgement based on individual clinical efficacy and safety. The primary endpoint was the difference in change in ESS scores between the pitolisant and placebo groups at 8 weeks. In both trials, superiority of pitolisant over placebo was tested first, then, if shown to be superior, the non-inferiority of pitolisant vs modafinil was tested based on a non-inferiority margin of 2 ESS points.
    - In HARMONY 1 (*Dauvilliers et al 2013*), 95 patients were randomized to receive pitolisant 10, 20, or 40 mg (expressed as salt form; equivalent to 8.9, 17.8, and 35.6 mg) per day; modafinil 100, 200, or 400 mg per day; or placebo. Of the 94 patients in the intent-to-treat (ITT) analysis, 81% had cataplexy, 45% had received psychostimulants (mostly modafinil or methylphenidate) and 35% were receiving anticataplectic drugs and continued them at stable doses during the trial (sodium oxybate, n = 8; antidepressants, n = 25).

- The primary analysis of between-group differences in mean ESS score at endpoint (adjusted for baseline) showed pitolisant to be superior to placebo (mean difference [MD] -3.0; 95% CI, -5.6 to -0.4; p = 0.024), but not non-inferior to modafinil (MD 0.12; 95% CI, -2.5 to 2.7; p = 0.250).
- A post-hoc analysis of ESS responder rate (final ESS score ≤ 10) showed a significantly greater response with pitolisant vs placebo (13 vs 45%; MD 4.4 [95% CI, 2.1 to 9.2]; p < 0.0006) and a similar response between pitolisant and modafinil (45 vs 46%; MD 1.0 [95% CI, 0.68 to 1.6]; p = 0.908).
- MWT values decreased from baseline in the placebo group but improved in the pitolisant group demonstrating superiority of pitolisant (MD 1.47; 95% CI, 1.01 to 2.14; p = 0.044). MWT also improved from baseline in the modafinil group. There was no statistically significant difference between pitolisant and modafinil (MD 0.77; 95% CI, 0.52 to 1.13; p = 0.173).
- NO GO error scores in the SART were similar between baseline and end of treatment in the placebo group, whereas they decreased in the pitolisant group, with a statistically significant difference between groups (p = 0.038). Changes in the modafinil and pitolisant groups were not statistically different (p = 0.765). There were no differences in changes from baseline between either pitolisant and placebo or pitolisant and modafinil in either the SART GO scores (p = 0.176, p = 0.141) or total SART scores (p = 0.053; p = 0.370).
- The European Quality-of-Life Questionnaire (EQ-5D) values were similar in all 3 groups, whereas patient global impression on treatment (PGO) improved only slightly more for pitolisant or modafinil than for placebo.
- In post-hoc analyses, pitolisant was superior to placebo (MD 0.38; 95% CI, 0.16 to 0.93; p = 0.034) but not non-inferior to modafinil (MD 0.54; 95% CI, 0.24 to 1.23; p = 0.138) for improvement in daily cataplexy rate from baseline.
- AEs occurred in 22 patients receiving pitolisant, 26 receiving modafinil, and 10 receiving placebo. The most frequent AEs were headache for the 3 groups; insomnia, abdominal discomfort, and nausea for pitolisant; and abdominal discomfort, nausea, diarrhea, dizziness, anxiety, and irritability for modafinil.

▪ HARMONY 1bis (unpublished) (*Wakix dossier 2019, Wakix FDA clinical review 2019*) compared pitolisant titrated to a maximum dose of 20 mg per day, modafinil 200 to 400 mg per day, and placebo in 166 patients. Of the 164 patients included in the extended ITT population, a history of cataplexy was present in 50 (75%) patients in the pitolisant group, 50 (77%) in the modafinil group, and 26 (81%) in the placebo group. Patients with severe cataplexy were allowed to remain on their anticataplectic medication at a stable dose except tricyclic antidepressants (TCAs).

- The pitolisant group had a significantly greater ESS score improvement from baseline compared with placebo, demonstrating superiority. The mean change from baseline in ESS score (± standard deviation [SD]) was -4.5 (4.6) for pitolisant and -3.7 (5.6) for placebo (treatment effect: -2.12; 95% CI, -4.10 to -0.14; p = 0.036). The mean change from baseline in ESS score (±SD) was -7.8 (5.8) for modafinil; the non-inferiority of pitolisant compared to modafinil could not be concluded (treatment effect: 2.83; 95% CI, 1.10 to 4.55; p = 0.002), most likely due to an imbalance between dosages of both drugs and the short treatment period.
  - The upper dose of pitolisant was limited to 20 mg daily (one-half the maximum dose allowed in other trials), while modafinil was titrated up to the recommended dosing of 200 mg or 400 mg daily.
- The ESS responder rate (final ESS score ≤ 10 or ESS score reduction ≥ 3) was significantly greater in the pitolisant group (64.2%) compared to the placebo group (34.4%) (RR 2.10; p = 0.002). There was no significant difference between pitolisant and modafinil (64.2% vs 76.9%; RR 0.86; p = 0.052).
- MWT values decreased from baseline in the placebo group but improved in the pitolisant group (p = 0.022). MWT also improved from baseline in the modafinil group; however, no statistically significant difference between pitolisant and modafinil was seen (p = 0.198).
- The NO GO error scores in the SART decreased in the pitolisant group, with a statistically significant treatment difference compared with placebo (p = 0.002); changes in the modafinil and pitolisant groups were not statistically different.
- Differences in weekly cataplexy rate (WCR) between pitolisant and placebo were not significant (MD -1.00; 95% CI, -2.12 to 0.13; p = 0.077), nor were the differences between pitolisant and modafinil (MD 0.05; 95% CI, -0.55 to 0.65; p = 0.865).
- The most frequent AEs were headache in all 3 groups; nausea, nasopharyngitis, and dizziness in the pitolisant group; nasopharyngitis in the modafinil group; and dizziness, diarrhea, insomnia, and fatigue in the placebo group.

○ The efficacy and safety of pitolisant on cataplexy in 106 patients with narcolepsy were evaluated in a DB, PC, MC RCT (HARMONY CTP; *Szakacs et al 2017*). Patients received 3 weeks of flexible dosing (5, 10, or 20 mg as determined by the investigator based on efficacy and tolerance) followed by 4 weeks of stable dosing (5, 10, 20, or 40 mg). The primary endpoint was the change in the average number of cataplexy attacks per week as recorded in patient diaries (ie, the WCR between the 2-week baseline period and the 4-week stable dosing period). The cataplexy reduction was measured by the ratio $WCR_{f/b} = WCR_f/WCR_b$.

- In the stable dosing phase, 64.8% of patients (35/54) in the pitolisant group received the maximum dose of 40 (35.6) mg.
- From a baseline WCR of 9.15 in the pitolisant group and 7.31 in the placebo group, the WCR was significantly reduced by a relative 75% in the pitolisant group (final WCR = 2.27; $WCR_{f/b}$ = 0.25) compared with 38% in the placebo group (final WCR = 4.52; $WCR_{f/b}$ = 0.62; rate ratio [rR] = 0.51; 95% CI, 0.44 to 0.60; p < 0.0001).
  - In post-hoc analyses, this effect remained significant (all p < 0.0001) for each subgroup of patients receiving 10 mg (n = 7), 20 mg (n = 9), or 40 mg (n = 35) as their stable dose.
  - In a pre-specified analysis, the effect of pitolisant was unchanged, irrespective of whether patients used concomitant anticataplectic treatment pre-inclusion. The geometric mean of the ratio $WCR_{f/b}$ for patients who were receiving concomitant anticataplectic treatment (rR 0.49; 95% CI, 0.31 to 0.82; n = 12) or did not receive this medication (rR 0.51; 0.11 to 2.28; n = 93) were not significantly different ($p_{interaction}$ = 0.455).
- For almost all secondary endpoints, a significant superiority of pitolisant was shown (ie, proportion of patients with WCR > 15 at the end of treatment, mean ESS decrease, patient proportion with final ESS ≤ 10, MWT mean change, CGI-C, PGO, and frequency of hallucinations).
- The proportion of patients reporting AEs did not differ significantly between those receiving pitolisant and those receiving placebo (31% for pitolisant vs 35% for placebo); however, double the number of AEs were considered treatment-related with pitolisant compared with placebo (28% for pitolisant vs 12% for placebo; p = 0.048). The most frequent AEs were headache for both treatment groups; irritability, anxiety, and nausea for the pitolisant group; and somnolence for the placebo group.

○ A 12-month, OL, MC, uncontrolled longitudinal study (HARMONY 3) was conducted to evaluate the long-term safety of pitolisant (*Dauvilliers et al 2019*). In addition, a 5-year extension of HARMONY 3 was conducted in the French cohort of patients. A total of 102 patients were treated. Sixteen patients were already treated through the authorization for temporary use (ATU) and 86 patients were naïve to pitolisant.

- In the 12-month analysis (N = 68; 34 prematurely withdrew), the mean change from baseline in ESS score (±SD) was -4.63 (4.91) and about two-thirds (44/68) of patients who completed the study were ESS responders (final ESS score ≤ 10 or ESS score reduction ≥ 3). On the CGI-C scale, investigators rated 94.1% of patients who completed 12 months of treatment as improved. The number of complete (generalized) cataplexy attacks per day decreased by 76% between baseline (0.33) and 12 months (0.08) in the subgroup of 44 patients with completed sleep diaries through the 12-month visit; the number of partial cataplexy attacks per day decreased by 65% between baseline (0.77) and 12 months (0.27). The most frequently reported treatment-emergent AEs (TEAEs) were headache (11.8%), insomnia (8.8%), weight gain (7.8%), anxiety (6.9%), depression (4.9%) and nausea (4.9%).
- In the 5-year extension, the decrease in ESS score (±SD) achieved by the study population at the end of the first 12-month period was maintained and continued during the extended follow-up period, with -4.41 (5.38) after 2 years of treatment (n = 45), -4.45 (6.16) after 3 years of treatment (n = 38), -4.76 (5.73) after 4 years of treatment (n = 34), and -6.07 (7.19) after 5 years of treatment (n = 14). The most commonly reported TEAEs were headache (19.5%), weight gain (18.2%), insomnia (11.7%), anxiety (11.7%), depression (11.7%), and nausea (11.7%) (*Wakix dossier 2019*).
- No new safety signals were identified during long-term exposure to pitolisant for up to 5 years compared with the safety profile identified in previous RCTs.

○ A postmarketing observation study in Europe is ongoing and will follow patients for up to 5 years. The AE profiles in these long-term studies, and in the European postmarketing databases, are similar to the AE profile observed during the short-term clinical trials. Of note, fewer than 100 patients with narcolepsy have received the proposed highest recommended dose of pitolisant (35.6 mg). However, narcolepsy is an orphan indication and no clear association between dose and AEs was evident from the narcolepsy clinical trials (*Wakix FDA summary review 2019*).

- Sodium oxybate/oxybate salts:

○ A systematic review and meta-analysis (N = 6 RCTs and 5 companion reports, N = 741) evaluated the efficacy and safety of sodium oxybate in narcolepsy-cataplexy patients (*Alshaikh et al 2012*). Included trials ranged from 4 to 12 weeks in duration. The dose of sodium oxybate was between 4.5 to 9 g per night in most of the studies. The primary endpoint was elimination of EDS according to subjective or objective indicators.

- Sodium oxybate (usually 9 g/night) was superior to placebo for reducing mean weekly cataplexy attacks (n = 2 RCTs, MD: -8.46, 95% CI, -15.27 to -1.64), heterogeneity: I^2 = 0%, test for overall effect: Z = 2.43 [p = 0.01]); increasing the MWT (n = 2 RCTs, MD: 5.18, 95% CI, 2.59 to 7.78, I^2 = 0%, Z = 3.93 [p < 0.0001]); and reducing sleep attacks (n = 2 RCTs, MD: -9.65, 95% CI, -17.72 to -1.59), I^2 = 13%, Z = 2.35 [p = 0.02]). Data from 3 RCTs indicated an increase in CGI-C scores (RR: 2.42, 95% CI, 1.77 to 3.32, I^2 = 0%, Z = 5.53 [p < 0.00001]). Sodium oxybate did not significantly increase REM sleep vs placebo (n = 2 RCTs, MD: -0.49, 95% CI, -3.90 to 2.92, I^2 = 0%, Z = 0.28 [p = 0.78]). Patients receiving sodium oxybate (9 g per night) experienced more AEs vs placebo,

including nausea (p < 0.00001), vomiting (p = 0.09), dizziness (p = 0.02) and enuresis (p = 0.03); most AEs were mild or moderate.

- A DB, PC, PG, MC RCT (N = 222) assessed the efficacy of sodium oxybate, modafinil, and the combination of the two for EDS in narcolepsy patients previously taking modafinil (*Black & Houghton 2006*). Patients received unchanged doses of modafinil (with sodium oxybate placebo) during a 2-week baseline phase. Following a baseline PSG and MWT, they were randomly assigned to 1 of 4 treatment groups: sodium oxybate placebo plus modafinil placebo, sodium oxybate plus modafinil placebo, modafinil plus sodium oxybate placebo, or sodium oxybate plus modafinil. Sodium oxybate was administered as 6 g nightly for 4 weeks and was then increased to 9 g nightly for 4 additional weeks. The primary endpoint was the MWT; secondary endpoints included ESS score and the CGI-C.
  - Following the switch from modafinil to placebo, the mean average daytime sleep latency on the MWT decreased from 9.74 minutes at baseline to 6.87 minutes after 8 weeks (p < 0.001). In the sodium oxybate group, there was no difference (from 11.29 to 11.97 minutes) suggesting that sodium oxybate was as effective as the previously administered modafinil. In contrast, the sodium oxybate-modafinil group demonstrated an increase in daytime sleep latency from 10.43 minutes to 13.15 minutes (p < 0.001), suggesting an additive effect. The sodium oxybate group also demonstrated a decrease in median average ESS scores, from 15 to 12.0, whereas the sodium oxybate-modafinil group decreased from 15.0 to 11.0 (p < 0.001 for each from baseline). In the sodium oxybate group, sleep attacks decreased from a mean of 10.05 at baseline to 7.10 after 8 weeks (p < 0.001) and the sodium oxybate-modafinil group demonstrated a decrease from 11.82 to 5.55 (p < 0.001). There was no significant difference between the modafinil- and placebo-treated groups. Compared with the placebo group, 48.0% (p = 0.002) of the sodium oxybate group and 46.3% (p = 0.023) of the sodium oxybate-modafinil group were judged to be much improved or very much improved on the GCI-C, compared with 21.8% in the placebo group and 19% in the modafinil group.
- Patients with narcolepsy-cataplexy (N = 55) who had received sodium oxybate for ≥ 6 months (range, 7 to 44 months, mean 21 months) in a long-term, OL sodium oxybate safety trial were enrolled in a DB treatment withdrawal study (*U.S. Xyrem Multicenter Study Group 2004*). Patients were previously stabilized on sodium oxybate using individualized doses providing optimum clinical effect, ranging from 3 to 9 g nightly. A 2-week single-blind (SB) sodium oxybate treatment phase established a baseline for the weekly occurrence of cataplexy. This was followed by a 2-week DB phase in which patients were randomized to receive unchanged drug therapy (n = 26) or placebo (n = 29). The primary endpoint was the change in the number of weekly cataplexy attacks from the baseline to the DB treatment phase.
  - In the sodium oxybate group, there was no median change in the number of cataplexy attacks between the 2-week SB baseline phase and the 2-week DB phase. In contrast, cataplexy attacks increased by a median of 21.0 in the placebo patients during the same 2-week period (p < 0.001); median change from baseline was 39.0 for the placebo group and 16.5 for the sodium oxybate group. The mean frequency of weekly cataplexy attacks over the 2-week baseline period increased from 15.8 to 46.4 at the end of the 2-week DB phase for patients receiving placebo; in patients receiving sodium oxybate, the number of cataplexy episodes was 9.9 and 12.8 at the same time points. There was no evidence of rebound cataplexy in patients who were randomized to placebo following long-term use of sodium oxybate. During the SB phase of the study, AEs were reported in 17 (31%) patients. During the DB phase, AEs were reported by 12 (22%) patients, including 3 patients in the sodium oxybate group, and 9 in the placebo group. No AE led to discontinuation and none were serious.
- The efficacy of sodium oxybate in the treatment of cataplexy and EDS in pediatric patients with narcolepsy was established in a DB, PC, randomized withdrawal (RW) study (*Plazzi et al 2018*). The study enrolled 106 pediatric patients 7 to 17 years of age with a baseline history of ≥ 14 cataplexy attacks in a typical 2-week period prior to any treatment for narcolepsy symptoms. The primary endpoint was change in weekly number of cataplexy attacks from the last 2 weeks of the stable-dose period (baseline) to the 2 weeks of the DB treatment period.
  - Ninety-six (92%) patients completed the stable-dose period, of whom 63 (the efficacy population) were randomly assigned to receive sodium oxybate (n = 31) or placebo (n = 32) for 2 weeks. A preplanned interim analysis of the primary endpoint showed efficacy (p = 0.0002), resulting in discontinuation of the placebo arm following guidance from the data safety monitoring board; 33 patients then received sodium oxybate on an OL basis during the DB period. Patients who were randomly assigned to receive placebo and who were withdrawn from sodium oxybate (32/63 [51%]) had increased weekly cataplexy attacks (median increase of 12.7 attacks per week [first quartile {Q1}, third quartile {Q3} = 3.4, 19.8]) when compared with those randomly assigned to continue treatment with sodium oxybate (median increase of 0.3 attacks per week [-1.0, 2.5]; p < 0.0001).
  - The median change from baseline in ESS-Child and Adolescent (CHAD) scores was greater in the placebo group (3.0 [Q1, Q3 = 1.0, 5.0]), indicating increased sleepiness, compared with the sodium oxybate group (0.0 [-1.0, 2.0]; p = 0.0004).
- The safety and efficacy of oxybate salts were evaluated in an unpublished Phase 3, DB, PC, RW, MC study in 201 adults with narcolepsy with cataplexy currently untreated or treated with or without anticataplectics (*Xywav dossier 2020)*. Enrollment criteria included a history of ≥ 14 cataplexy attacks in a typical 2-week period prior to receiving

any narcolepsy treatment. The study included a 12-week, OL, optimization and titration period to transition patients to oxybate salts; a 2-week stable-dose period; a 2-week DB, RW period; and a 2-week safety follow-up. During the withdrawal period, patients were randomized 1:1 to placebo or to continue oxybate salts. The primary endpoint was the change in the weekly number of cataplexy attacks from the time during the 2 weeks of the stable-dose period to the time during the 2 weeks of the DB, RW period, as determined from patients' daily diaries. The key secondary endpoint was the change in the ESS score from the end of the stable-dose period to the end of the DB, RW period.
    - Prior to randomization, the median (Q1, Q3) number of weekly cataplexy attacks did not differ in patients randomized to placebo (1.1 [0.0, 7.9]) vs those who continued oxybate salts (1.0 [0.0, 4.4]). During the DB, RW period, patients randomized to continue oxybate salts experienced no change (median [interquartile range {IQR}], mean [SD]) in the weekly frequency of cataplexy attacks, while patients randomized to discontinue oxybate salts and take placebo experienced an increase in cataplexy attacks (median [Q1, Q3]: 0.0 [-0.5, 1.7], mean [SD]: 0.12 [5.77] vs 2.4 [0.0,11.6], mean [SD]: 11.46 [24.75] respectively; treatment difference, $p < 0.0001$).
    - Prior to randomization, the median (Q1, Q3) ESS score did not differ in oxybate salts-treated patients who were randomized to placebo vs those who continued oxybate salts treatment (13.0 [9.0, 17.0] vs 14.0 [10.0, 19.0], respectively). At the end of the DB, RW period, the change in median (Q1, Q3) ESS score from baseline for patients randomized to placebo vs oxybate salts was 2.0 (0.0, 5.0) vs 0.0 (-1.0, 1.0), respectively.
  - Oxybate salts have not been specifically studied in a pediatric clinical trial. Use of oxybate salts in pediatric patients ≥ 7 years of age with narcolepsy is supported by evidence from an adequate and well-controlled study of sodium oxybate in pediatric patients 7 to 17 years of age (*Plazzi et al 2018*, see above), a study in adults showing a treatment effect of oxybate salts similar to that observed with sodium oxybate (see above), pharmacokinetic (PK) data of sodium oxybate from adult and pediatric patients, and PK data of oxybate salts from healthy adult volunteers (*Xywav dossier 2020*).
- Solriamfetol:
  - The approval of solriamfetol was based on data from the Treatment of Obstructive sleep apnea and Narcolepsy Excessive Sleepiness (TONES) Phase 3 clinical program, which included 4 PC RCTs.
  - TONES 2 was a12-week, Phase 3, DB, PC, MC RCT (N = 239) that evaluated the safety and efficacy of solriamfetol in the treatment of type 1 or type 2 narcolepsy (*Thorpy et al 2019*). Patients were randomized to solriamfetol 75, 150, or 300 mg once daily. The co-primary endpoints were change from baseline to week 12 in mean sleep latency assessed by the MWT and ESS score. Improvement on the PGI-C was the key secondary endpoint.
    - Statistical significance was met for the co-primary endpoints and the PGI-C for the 150 and 300 mg doses, but not the 75 mg dose. At week 12, the least squares (LS) mean change from baseline on the MWT showed an increase in sleep latency of 12.3 and 9.8 minutes for 150 and 300 mg, respectively vs 2.1 minutes with placebo ($p < 0.0001$) (LS mean differences vs placebo: 10.1 [95% CI, 6.4 to 13.9] and 7.7 [95% CI, 4.0 to 11.3]). For the ESS score, the LS mean change from baseline at week 12 was -6.4, -5.4, and -3.8 for the 300 mg, 150 mg, and 75 mg doses of solriamfetol, respectively, and -1.6 with placebo (LS mean differences vs placebo: -4.7 [95% CI, -6.6 to -2.9]; $p < 0.0001$, -3.8 [95% CI, -5.6 to -2.0]; $p< 0.0001$, and -2.2 [95% CI, -4.0 to -0.3]; $p = 0.0211$). At week 12, higher percentages of patients treated with solriamfetol 150 mg (78.2%) and 300 mg (84.7%) reported PGI-C improvement vs placebo (39.7%; both $p < 0.0001$).
  - TONES 3 was a 12-week, Phase 3, DB, PC, MC RCT (N = 476) that evaluated the safety and efficacy of solriamfetol for the treatment of EDS in patients with OSA with current or prior sleep apnea treatment (*Schweitzer et al 2019*). Patients were randomized to solriamfetol 37.5, 75, 150, or 300 mg once daily. The co-primary endpoints were change from baseline to week 12 in mean sleep latency assessed by the MWT and ESS score. Improvement on the PGI-C was the key secondary endpoint.
    - The co-primary endpoints of change from baseline at week 12 in MWT and ESS were met at all solriamfetol doses, and the key secondary endpoint of PGI-C was met at all doses except the 37.5 mg dose. At week 12, the LS mean differences from placebo for solriamfetol 300, 150, 75, and 37.5 mg were 12.8 [95% CI, 10 to 15.6], 10.7 [95% CI, 8.1 to 13.4], 8.9 [95% CI, 5.6 to 12.1], and 4.5 [95% CI, 1.2 to 7.9] minutes, respectively ($p < 0.0001$ for 300, 150, and 75 mg; $p = 0.085$ for 37.5 mg). For the ESS score, the LS mean differences from placebo were -4.7 [95% CI, -5.9 to -3.4], -4.5 [95% CI,-5.7 to -3.2], -1.7 [95% CI, -3.2 to -0.2], and -1.9 [95% CI, -3.4 to -0.3], respectively ($p < 0.0001$ for 300 and 150 mg; $p = 0.0233$ for 75 mg; $p = 0.061$ for 37.5 mg). At week 12, higher percentages of patients on solriamfetol 75 mg (72.4%; $p < 0.05$), 150 mg (89.7%; $p < 0.0001$), and 300 mg (88.7%; $p < 0.0001$) reported overall improvement on the PGI-C vs placebo (49.1%).
  - TONES 4 was a Phase 3, DB, PC, MC RW study that evaluated the maintenance of efficacy and safety of solriamfetol vs placebo for the treatment of EDS in adults with OSA (*Strollo et al 2019*). After 2 weeks of clinical titration (n = 174, 75 mg once daily starting dose, titrated up or down every 3 days to 75, 150, or 300 mg) and 2 weeks of stable dose administration (n = 148), patients who reported much or very much improvement on the PGI-C and had numerical improvements on the MWT and ESS were randomly assigned to placebo or solriamfetol for 2 additional weeks.

- From baseline to week 4, mean MWT sleep latencies improved from 12.3 to 13.1 minutes to 29.0 to 31.7 minutes, and ESS scores improved from 15.3 to 16.0 to 5.9 to 6.4. Patient-reported EDS decreased from ~15 to 16 to ~6, which is within the normal range. From weeks 4 to 6 (RW phase), solriamfetol-treated patients maintained improvements in MWT and ESS. The LS mean change in MWT mean sleep latency was -12.1 minutes with placebo compared with -1.0 minute with solriamfetol; LS mean difference between solriamfetol and placebo was 11.2 minutes (95% CI, 7.8 to14.6; p < 0.0001). The LS mean changes in ESS scores were 4.5 and -0.1 for placebo and solriamfetol, respectively, resulting in an LS mean difference of -4.6 (95% CI, -6.4 to -2.8; p < 0.0001). During the RW phase, a statistically significant 50.0% of patients who were switched to placebo reported worsening on the PGI-C relative to 20.0% who continued using solriamfetol (-30.0; 95% CI, -46.0 to -14.0; p < 0.001). Similarly, 59.0% of patients switched to placebo worsened, as rated by the physicians on the CGI-C, vs 21.7% who continued using solriamfetol (-37.3; 95% CI, -53.50 to -21.19; p < 0.0001).

- TONES 5 was a Phase 3 OL extension study that evaluated the long-term safety and maintenance of efficacy of solriamfetol for up to 52 weeks in the treatment of patients with narcolepsy or OSA who completed previous trials of solriamfetol (*Malhotra et al 2019*, *Sunosi dossier 2019*). In a 2-week OL titration phase, patients were initiated on solriamfetol 75 mg, titrated to a maximum tolerated dose of 150 or 300 mg, followed by a maintenance phase. During a 2-week PC RW phase ~ 6 months later, patients were randomized either to placebo or to continue solriamfetol at their dose of 75 mg, 150 mg, or 300 mg for 2 weeks. The primary endpoint was change in ESS score during the RW phase.
  - The LS mean change from the beginning to the end of the RW phase for the ESS score was 1.6 with solriamfetol compared with 5.3 with placebo, resulting in an LS mean difference of -3.7 (95% CI, -4.80 to -2.65; p < 0.0001). Similar results were seen in the subgroup analysis of patients with OSA and patients with narcolepsy. The percentage of patients who were reported as worse on the PGI-C at the end of the RW phase was 64.5% for patients randomized to placebo compared to 28.2% for patients on solriamfetol (p < 0.0001). Long-term maintenance of efficacy of solriamfetol was demonstrated by sustained reductions in ESS scores in Group A (12-week narcolepsy or OSA study) for up to 40 weeks and in Group B (Phase 2 studies or 6-week Phase 3 study) for up to 52 weeks. During the RW period, patients did not demonstrate rebound sleepiness or withdrawal after abrupt discontinuation of solriamfetol.

Place in Therapy

- Narcolepsy:
  - The 2007 American Academy of Sleep Medicine (AASM) practice parameters for the treatment of narcolepsy and other hypersomnias of central origin (*Morgenthaler et al 2007a*) recommend pharmacologic therapy based on the diagnosis and targeted symptoms. Most of the agents used to treat EDS have little effect on cataplexy or other REM sleep associated symptoms, while most antidepressants and anticataplectics have little effect on alertness; however, some medications act on both symptoms. Co-administration of 2 or more drug classes may be required in some patients to adequately address their symptoms. Scheduled naps may be beneficial, but seldom suffice as primary therapy for narcolepsy. The guidelines state that modafinil is effective for treatment of EDS due to narcolepsy and sodium oxybate is effective for treatment of cataplexy, EDS, and disrupted sleep due to narcolepsy. Sodium oxybate may be effective for treatment of hypnagogic hallucinations and sleep paralysis. Amphetamine, methamphetamine, dextroamphetamine, and methylphenidate are effective for treatment of EDS due to narcolepsy. Antidepressants (TCAs, selective serotonin reuptake inhibitors [SSRIs], venlafaxine) may be effective for treatment of cataplexy. TCAs, SSRIs, and venlafaxine may be effective treatment for sleep paralysis and hypnagogic hallucinations.
  - The European Academy of Neurology (EAN) 2011 guidelines on management of narcolepsy in adults (*Billiard et al 2011*) recommend modafinil as the first-line treatment for EDS associated with narcolepsy when EDS is the most disturbing symptom. Sodium oxybate is recommended when EDS, cataplexy, and poor sleep coexist. The guideline notes that the combination of modafinil and sodium oxybate may be more effective than sodium oxybate alone. Methylphenidate may be an option if the response to modafinil is inadequate; sodium oxybate is not recommended. Naps are best scheduled on a patient-by-patient basis.
  - While armodafinil has been shown in clinical studies to be effective for EDS in narcolepsy, its specific place in therapy is not discussed in the current guidelines.
- OSA:
  - The 2006 AASM practice parameters for the medical therapy of OSA (*Morgenthaler et al 2006*) provide recommendations for patients with OSA who do not adapt well to or respond to initial therapy with CPAP, oral appliances, or surgical modification. Dietary weight loss in obese individuals may be beneficial and should be combined with a primary treatment for OSA. Modafinil is recommended for the treatment of residual EDS in OSA patients who have sleepiness despite effective PAP treatment and who are lacking any other identifiable cause for their sleepiness.
- SWD:

- The AASM practice parameters for the clinical evaluation and treatment of circadian rhythm sleep disorders (*Morgenthaler et al 2007b*) recommend planned napping before or during the night shift to improve alertness and performance in patients with SWD. Timed light exposure in the work environment and light restriction in the morning, when feasible, is indicated to decrease sleepiness and improve alertness during night shift work. Administration of melatonin prior to daytime sleep is indicated to promote daytime sleep among night shift workers. Hypnotic medications may be used to promote daytime sleep among night shift workers. Carryover of sedation to the nighttime shift with potential adverse consequences for nighttime performance and safety must be considered. Modafinil is indicated to enhance alertness during the night shift for SWD. Caffeine is indicated to enhance alertness during the night shift for SWD.

Safety

- Modafinil/armodafinil:
  - Warnings and precautions of modafinil/armodafinil include rare serious skin reactions including Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN); drug rash with eosinophilia and systemic symptoms (DRESS); multiorgan hypersensitivity; angioedema and anaphylaxis reactions; persistent sleepiness; psychiatric AEs; and CV AEs including chest pain, palpitations, dyspnea, and transient ischemic T-wave changes on electrocardiogram (ECG) in association with mitral valve prolapse or left ventricular hypertrophy. Increased monitoring of heart rate and blood pressure (BP) may be appropriate in patients receiving modafinil/armodafinil. Caution should be exercised when these drugs are prescribed to patients with known CV disease.
  - The most common AEs (≥ 5%) with armodafinil vs placebo were headache (17 vs 9%), nausea (7 vs 3%), dizziness (5 vs 2%), and insomnia (5 vs 1%).
  - The most common AEs (≥ 5%) with modafinil vs placebo were headache (34 vs 23%), nausea (11 vs 3%), nervousness (7 vs 3%), rhinitis (7 vs 6%), diarrhea (6 vs 5%), back pain (6 vs 5%), anxiety (5 vs 1%), insomnia (5 vs 1%), dizziness (5 vs 4%), and dyspepsia (5 vs 4%).
- Pitolisant:
  - Pitolisant is contraindicated in patients with severe hepatic impairment and has not been studied in these patients. Pitolisant is extensively metabolized by the liver and there is a significant increase in pitolisant exposure in patients with moderate hepatic impairment.
  - Pitolisant has a warning for QT prolongation. Use should be avoided with other drugs known to prolong the QT interval. Pitolisant should also be avoided in patients with a history of cardiac arrhythmias, as well as other circumstances that may increase the risk of the occurrence of torsade de pointes or sudden death, including symptomatic bradycardia, hypokalemia or hypomagnesemia, and the presence of congenital prolongation of the QT interval. Patients with hepatic or renal impairment should be monitored for increased QTc.
  - In the PC trials, the most common AEs (occurring in ≥ 5% of patients and at twice the rate of placebo) with the use of pitolisant were insomnia (6%), nausea (6%), and anxiety (5%).
- Solriamfetol:
  - Solriamfetol is contraindicated with concomitant use of monoamine oxidase inhibitors (MAOIs), or within 14 days following discontinuation of an MAOI because of the risk of hypertensive reaction.
  - Warnings and precautions of solriamfetol include BP and heart rate increases and psychiatric symptoms such as anxiety, insomnia, and irritability.
  - The most common AEs (≥ 5% and greater than placebo) in either the narcolepsy or OSA populations vs placebo were headache (16 vs 7%), nausea (7 vs 4%), decreased appetite (9 vs 1%), insomnia (5 vs 4%), and anxiety (6 vs 1%).
- Sodium oxybate/oxybate salts:
  - Sodium oxybate/oxybate salts are contraindicated in combination with sedative hypnotics or alcohol and in patients with succinic semialdehyde dehydrogenase deficiency, a rare inborn error of metabolism.
  - Sodium oxybate/oxybate salts carries a boxed warning concerning CNS depression and the potential for misuse/abuse. Abuse or misuse of illicit GHB is associated with CNS AEs, including seizure, respiratory depression, decreased consciousness, coma, and death.
  - Because of the risks of CNS depression and abuse and misuse, sodium oxybate/oxybate salts are available only through a restricted distribution program under a risk evaluation and mitigation strategies (REMS). Prescribers must be specially certified, and the drug may be dispensed only by a central pharmacy that is specially certified.
  - Other warnings and precautions include respiratory depression and sleep disordered breathing; depression and suicidality; parasomnias; and use in patients sensitive to high sodium intake due to the high salt content (sodium oxybate only).
  - The most common AEs with sodium oxybate in adults (≥ 5% and at least twice the incidence with placebo) were nausea, dizziness, vomiting, somnolence, enuresis, and tremor.
  - The most common AEs with oxybate salts in adults (≥ 5%) were headache, nausea, dizziness, decreased appetite, parasomnia, diarrhea, hyperhidrosis, anxiety, and vomiting.

- The most common AEs in pediatric patients in the oxybate salts RW trial (≥ 5%) were enuresis, nausea, headache, vomiting, weight decreased, decreased appetite, and dizziness.

Dosing

- Armodafinil:
  - Narcolepsy/OSA: 150 mg to 250 mg orally once daily in the morning
    - OSA: up to 250 mg once daily has been well tolerated, but there is no consistent evidence that this dose confers additional benefit beyond the 150 mg dose
  - SWD: 150 mg orally once daily approximately 1 hour prior to the start of the work shift
  - Hepatic impairment: dose should be reduced in patients with severe hepatic impairment
- Modafinil:
  - Narcolepsy/OSA: 200 mg orally once daily in the morning
  - SWD: up to 400 mg once daily has been well tolerated, but there is no consistent evidence that this dose confers additional benefit beyond the 200 mg/day dose
  - Hepatic impairment: dose should be reduced to one-half in patients with severe hepatic impairment
- Pitolisant:
  - Recommended dosage range: 17.8 mg to 35.6 mg per day administered once daily upon awakening.
    - Dose titration as follows:
      - Starting dose: 8.9 mg (two 4.45 mg tablets) once daily
      - Increase dose to 17.8 mg (one 17.8 mg tablet) once daily
      - May increase to a maximum of 35.6 mg (two 17.8 mg tablets) once daily
      - Dose may be adjusted based on tolerability
      - It may take up to 8 weeks for some patients to achieve a clinical response
  - Hepatic and renal impairment: dose adjustments recommended in hepatic and renal impairment; not recommended in patients with end-stage renal disease (ESRD)
    - Moderate hepatic impairment: 8.9 mg once daily, increased after 14 days to a maximum dosage of 17.8 mg once daily.
    - Moderate and severe renal impairment: 8.9 mg once daily, increased after 7 days to a maximum dosage of 17.8 mg once daily.
  - Poor cytochrome P450 (CYP) 2D6 metabolizers: dose should be initiated at 8.9 mg once daily and titrated to a maximum dose of 17.8 mg once daily after 7 days.
  - Co-administration with strong CYP2D6 inhibitors and strong CYP3A4 inducers: dose adjustments recommended (see prescribing information)
- Sodium oxybate/oxybate salts:
  - Adult dosing:
    - Starting dose: 4.5 g per night orally, divided into 2 doses: 2.25 g at bedtime and 2.25 g taken 2.5 to 4 hours later, increased by 1.5 g per night at weekly intervals (additional 0.75 g at bedtime and 0.75 g taken 2.5 to 4 hours later) to the effective dosage range of 6 to 9 g per night orally
  - Pediatric dosing:
    - Starting dose, titration regimen, and maximum dose: weight-based, administered twice nightly; titrated gradually based on efficacy and tolerability
  - Patients transitioning from sodium oxybate to oxybate salts should initiate therapy at the same dose and regimen as sodium oxybate (g for g).
  - Hepatic impairment: dose should be reduced to one-half of the original dosage per night, divided into 2 doses
  - Co-administration with divalproex sodium: dose of divalproex sodium should be reduced by ≥ 20% in patients already stabilized on sodium oxybate/oxybate salts; a lower starting dose should be used when introducing sodium oxybate/oxybate salts in patients already taking divalproex sodium.
- Solriamfetol:
  - Narcolepsy:
    - Starting dose: 75 mg once daily
    - Recommended dose range: 75 to 150 mg once daily, doubled at intervals ≥ 3 days based on efficacy and tolerability
    - Maximum recommended dose: 150 mg once daily
  - OSA:
    - Starting dose: 37.5 mg once daily
    - Recommended dose range: 37.5 to 150 mg once daily, doubled at intervals of ≥ 3 days based on efficacy and tolerability
    - Maximum recommended dose: 150 mg once daily
  - Renal impairment: dose adjustments required; not recommended in patients with ESRD

Conclusion

- Current treatment options for EDS in narcolepsy include modafinil, armodafinil, pitolisant, solriamfetol, sodium oxybate, oxybate salts, and amphetamine derivatives, thus providing several agents with differing mechanisms of action. Many patients with narcolepsy may require treatment with more than 1 drug class to manage co-existing symptoms. Pitolisant and sodium oxybate/oxybate salts are also FDA-approved for treatment of cataplexy in adults with narcolepsy. Antidepressants such as SSRIs or venlafaxine (used off-label) may be effective for treatment of cataplexy and provide a first- or second-line option. Modafinil, armodafinil, and solriamfetol are also indicated for EDS in patients with OSA, while modafinil and armodafinil are also indicated for SWD.
- Modafinil is generally considered the first-line pharmacologic therapy for narcolepsy. Its efficacy is well established and illicit use is uncommon. There are no apparent clinical advantages of the longer half-life enantiomer, armodafinil, over the racemic mixture, modafinil. These agents have not been compared head-to-head with CNS stimulants, such as dextroamphetamine or methylphenidate. Therapeutic benefits of modafinil and amphetamine derivatives become apparent within days. However, CNS stimulants have limited efficacy data, are associated with high abuse potential, and are associated with more AEs than modafinil/armodafinil. Modafinil/armodafinil may be beneficial for the treatment of OSA patients with residual EDS despite effective conventional treatment. Modafinil/armodafinil have warnings for rare serious skin reactions, angioedema/anaphylaxis, and multiorgan hypersensitivity; caution should be exercised in patients with known CV disease and increased monitoring of BP and heart rate may be appropriate for patients receiving these agents. Modafinil/armodafinil is a substrate, inducer, and inhibitor of CYP450 isoenzymes, resulting in the potential for drug interactions, including reduced efficacy of oral contraceptives. Modafinil/armodafinil have demonstrated variable efficacy for SWD in clinical trials and AEs may outweigh benefits in some patients.
- Pitolisant, a novel H_3 receptor antagonist/inverse agonist, was FDA-approved in August 2019 for the treatment of EDS in adults with narcolepsy and gained the expanded indication for treatment of cataplexy in adults with narcolepsy in October 2020. In two 8-week pivotal RCTs vs placebo and modafinil active control in patients with narcolepsy (a majority of whom had co-existing cataplexy), pitolisant appeared to have similar efficacy to modafinil for improving EDS. In HARMONY 1, a post-hoc analysis indicated that pitolisant reduced daily cataplexy episodes significantly more than placebo but not more than modafinil. In HARMONY 1bis, differences in WCR between pitolisant and placebo were not significant, nor were the differences between pitolisant and modafinil. In the HARMONY CTP trial in narcolepsy patients with severe cataplexy, pitolisant demonstrated a relative reduction in WCR of 75% vs 38% with placebo; improvements were also seen in ESS scores, MWT, and frequency of hallucinations. Differences in dosing titration and dosing ranges may have partially accounted for the lack of effect on cataplexy seen in HARMONY 1 and HARMONY 1bis as compared with HARMONY CTP. A dose-response analysis was not performed in these trials (*Wakix FDA clinical review 2019*).
  - Pitolisant requires a 3-week dose titration and may take up to 8 weeks to achieve a clinical response. Pitolisant does not appear to have significant abuse potential and is the only unscheduled narcolepsy agent. Pitolisant is generally well tolerated and has not been associated with CV AEs or vital sign changes; the most common AEs were headache, insomnia, and nausea. Although some patients in the pitolisant trials were receiving concomitant medication(s) targeting narcolepsy and/or cataplexy, trials specifically evaluating pitolisant in combination with other narcolepsy agents are lacking. Pitolisant is contraindicated in patients with severe hepatic impairment and has a warning for QT prolongation. Pitolisant is metabolized by CYP2D6 and CYP3A4 and has the potential for multiple drug interactions, including some antidepressants. Like modafinil/armodafinil, pitolisant may decrease the efficacy of oral contraceptives. Limited long-term safety and efficacy data are available, particularly at the highest recommended dose. A DB, PC RCT is currently ongoing to assess the safety and efficacy of pitolisant in children 6 to < 18 years of age with narcolepsy with or without cataplexy (*Clinicaltrials.gov Web site*).
- Sodium oxybate/oxybate salts have demonstrated efficacy in reducing EDS and cataplexy in patients with narcolepsy; however, use of these agents presents several challenges. Full therapeutic response may require several weeks to manifest and the dose must be titrated slowly; the split dosing regimen requires patients to wake during the night to administer a second dose. Use of sodium oxybate/oxybate salts is limited by abuse and drug diversion potential, CNS depression, and REMS requirement. Medications that suppress cataplexy often improve sleep paralysis and hypnagogic hallucinations, although these symptoms do not usually require pharmacologic therapy (*Scammell 2020b*). In narcolepsy patients with co-existing EDS, cataplexy, and disrupted nocturnal sleep, sodium oxybate/oxybate salts are the only agents that are effective for all 3 manifestations. They are also the only agents currently indicated for pediatric patients. Data have shown that the combination of modafinil and sodium oxybate may be more effective for the treatment of EDS than sodium oxybate alone. Oxybate salts may be preferred over sodium oxybate to lower daily sodium load in narcolepsy patients with comorbid conditions sensitive to salt intake, such as HTN, HF, or renal impairment.
- Solriamfetol demonstrated efficacy vs placebo for the treatment of EDS in narcolepsy and OSA in 4 RCTs and maintenance of efficacy in an OL extension trial of up to 52 weeks. The placebo subtracted change in sleep latency assessed by the MWT from baseline to end of treatment ranged from 10 to 13 minutes (out of a possible 40 minutes),

a statistically and clinically meaningful treatment effect. However, there are no head-to-head trials with other established narcolepsy agents. The onset of effect of solriamfetol became apparent within 1 week of initiation in clinical trials. Solriamfetol's main safety concern is the potential for BP and heart rate increases, which may be of particular concern in patients with narcolepsy or OSA who already often have CV risk factors such as HTN, diabetes, dyslipidemia, and obesity. In contrast to modafinil/armodafinil and pitolisant, solriamfetol lacks the concern for potential reduced efficacy of concomitant oral contraceptives.

BACKGROUND

Narcolepsy

- Narcolepsy is a rare chronic neurological disorder of hypersomnia that results from dysregulation of the sleep/wake cycle and intrusion of sleep into wakefulness. Its associated symptoms are potentially debilitating to patients.
- Narcolepsy results from the loss of the neuropeptides, orexin-A and orexin-B (also known as hypocretin-1 and hypocretin-2). These neurotransmitters are products of the prepro-orexin gene and are made by neurons in the lateral hypothalamus. Orexin-A and -B have excitatory effects when they bind the ox1 and ox2 receptors on postsynaptic neurons. The orexins are released during wakefulness and increase the activity of many brain regions involved in the promotion of wakefulness, including the locus coeruleus, raphe nuclei, and tuberomammillary nucleus. By increasing the activity of these wake-promoting aminergic neurons, orexins stabilize wakefulness, prevent inappropriate transitions into REM or non-REM sleep, and inhibit REM sleep. Loss of orexins may allow REM sleep-related phenomena (eg, cataplexy, hypnagogic hallucinations, and sleep paralysis) to intrude into wakefulness (*Scammell 2019a*).
- Narcolepsy is typically classified as type 1 (narcolepsy with cataplexy, Na-1) or type 2 (narcolepsy without cataplexy, Na-2). Na-1 results from a loss of cerebrospinal fluid (CSF) orexin-A concentration, whereas Na-2 does not involve low levels of CSF orexin-A (*Bhattarai & Sumerall 2017, Scammell 2020a, Szabo et al 2019*). Na-1 is estimated to have a prevalence of 25 to 50 per 100,000 people. Narcolepsy typically begins in the teens and early twenties, but occasionally occurs as early as age 5 or after age 40. The prevalence of Na-2 is uncertain, as it is less well studied and more difficult to diagnose; however, it has been estimated as 20 to 34 per 100,000 people (*Scammel 2020a*). Males and females are equally affected (*Bhattarai & Sumerall 2017, Sunosi dossier 2019, Szabo et al 2019*).
- EDS is present in all patients with narcolepsy. EDS is characterized by chronic pervasive sleepiness and sleep attacks/inadvertent naps triggered by overwhelming urges to sleep (*Sunosi dossier 2019*). Other symptoms include cataplexy, hypnagogic hallucinations, and sleep paralysis; however, only about one-third of patients have all 4 symptoms (*Scammell 2020a*). A 2013 survey of narcolepsy patients indicated that EDS is the most disabling symptom experienced in their daily lives (*Sunosi FDA summary review*).
- EDS is not specific to narcolepsy and can be due to habitual loss of nighttime sleep, sleep fragmentation, a circadian sleep-wake disorder, a primary neurological disorder, or sedating drugs. In narcolepsy, sleepiness is characterized by a daily underlying irresistible drive for sleep that is associated with impaired cognitive ability, reduced psychosocial functioning and QoL that puts patients at risk of work-related, home, or automobile accidents (*Szabo et al 2019*).
- EDS is typically the first presenting symptom of narcolepsy. All patients with narcolepsy have chronic sleepiness, but they do not sleep more than healthy individuals during a 24-hour period (*Scammell 2020a*). EDS is routinely accompanied by sleep attacks, which are abrupt involuntary sleep episodes lasting from a few seconds to several minutes.
- Sleep paralysis has been described as the disturbing temporary inability to move voluntary muscles at sleep-wake transitions and usually occurs at the point of waking, although it may also occur just before falling asleep. Episodes of sleep paralysis can be frightening because the immobility may be accompanied by hypnopompic hallucinations or a sensation of suffocation (*Bhattarai & Sumerall 2017, Scammell 2020a*).
- Hypnagogic hallucinations are vivid, often frightening visual, tactile, or auditory hallucinations that occur while falling asleep. They probably result from a mixture of wakefulness and the dreaming of REM sleep (*Scammell 2019a*).
- Cataplexy is emotionally-induced transient muscle weakness that manifests as limb, head, or facial weakness. Episodes of cataplexy develop over several seconds and patients remain conscious regardless of the varying duration and severity that may occur. Severe episodes can result in bilateral weakness or paralysis, causing the patient to collapse (*Scammel 2020a, Szabo et al 2019*).
  - Up to 60% of patients with narcolepsy have cataplexy. Cataplexy is usually triggered by positive emotions such as laughing, joking, or excitement and less frequently by negative emotions such as anger or frustration.
- Many patients with narcolepsy fall asleep rapidly but have substantial fragmentation in nocturnal sleep. This sleep maintenance insomnia seems paradoxical in a disorder characterized by EDS, and it may reflect a low threshold to transition from sleep to wakefulness (*Bhattarai & Sumerall 2017, Scammell 2020a)*.
- Non-pharmacologic interventions may be of benefit for patients with narcolepsy (*Scammell 2020b*).
  - Regular napping may be sufficient for occasional patients, but most require pharmacologic therapy to reduce sleepiness and cataplexy. One or 2 well-timed, 20-minute naps may improve sleepiness, though some patients may require long naps. Specifically, a short nap around 1:00 or 2:00 PM is often helpful as it can improve alertness for 1

to 3 hours, reducing the need for stimulants in the afternoon. If possible, a brief nap at work or school is often helpful. Medications that may worsen daytime sleepiness (eg, opiates, benzodiazepines, alcohol, antipsychotics) should be avoided. Other medications such as theophylline or excessive caffeine intake may worsen insomnia, contributing to daytime sleepiness. Prazosin and other α-1 antagonists can worsen cataplexy.
  - Patients with narcolepsy are at increased risk for psychiatric co-morbidities, particularly depression and anxiety; have higher than expected rates of hypertension; and increased rates of obesity and diabetes. Thus, psychosocial support and regular screening for depression, hypertension, and obesity are important for patients with narcolepsy.
- Pharmacological interventions are the most common approach for treating narcolepsy. Current medications have been developed to target symptoms; however, most patients do not experience complete resolution despite receiving optimal standard treatment (*Bhattarai & Sumerall 2017, Scammell 2020b).*
- The goal of pharmacologic therapy is to improve alertness and thus performance and safety of important tasks and activities like school or work (*Scammell 2020b*).
  - Many sleep disorders (eg, sleep apnea, periodic leg movements) can coexist with narcolepsy, thereby contributing to symptoms. Such disorders should be addressed before initiating narcolepsy-specific medications.
  - Most of the drugs available to treat narcolepsy target either EDS or cataplexy. Thus, many patients who have both symptoms require more than 1 drug to manage their disease.
  - Since all patients with narcolepsy have some degree of EDS, most require a wakefulness-promoting medication. These agents improve performance (measured by reaction time and simulated driving tasks), but their ability to maintain wakefulness rarely exceeds 70 to 80% of normal. Currently available agents include modafinil/armodafinil and CNS stimulants such as methylphenidate or amphetamines. All are effective; however, modafinil is usually used as first-line therapy since it has been studied in PC RCTs and is associated with fewer AEs than traditional stimulants.
  - About 30% of narcolepsy patients have cataplexy that is substantial enough to warrant treatment. A REM-suppressing medication such as venlafaxine, fluoxetine, atomoxetine (all off-label) may be chosen as first-line agent; sodium oxybate, the sodium salt of GHB, is usually reserved for second-line use in patients who do not respond to these medications. The full therapeutic effect of sodium oxybate may require several weeks of treatment, while the benefit of amphetamines and modafinil become apparent within a few days. AEs of sodium oxybate are more common than with other medications used to treat narcolepsy. Sodium oxybate has the potential for abuse and dependence and is only available through a REMS program.

<u>OSA</u>
- OSA is a chronic disorder that is characterized by obstructive apneas and hypopneas caused by repetitive collapse of the upper airway during sleep. The diagnosis should be considered whenever a patient presents with symptoms such as EDS, snoring, and choking or gasping during sleep, particularly in the presence of risk factors such as obesity, male gender, and advanced age (*Kline 2019*).
  - The most common symptoms of OSA are daytime sleepiness and nocturnal snoring or “choking.” Approximately 20% of patients with OSA have EDS (*Sunosi dossier 2019*).
  - Other symptoms and signs may be suggestive of OSA. For example, sleep maintenance insomnia with repetitive awakenings should prompt consideration of OSA. Some patients with OSA complain of insomnia rather than daytime sleepiness because they are unable to maintain sleep; this phenomenon may be more common in females.
  - Morning headaches are reported by 10 to 30% of patients with untreated OSA. They are usually bifrontal and squeezing in quality, with no associated nausea, photophobia, or phonophobia. They typically occur daily or most days of the week and may last for several hours after awakening in the morning. The cause of the headaches is not well established and may be multifactorial; proposed mechanisms include hypercapnia, vasodilation, increased intracranial pressure, and impaired sleep quality.
  - Other associated symptoms and historical features include the following:
    - Awakening with a sensation of choking, gasping, or smothering
    - Awakening with a dry mouth or sore throat
    - Moodiness or irritability
    - Lack of concentration
    - Memory impairment
    - Decreased libido and impotence
    - Nocturia
    - Awakening with angina pectoris
    - History of hypertension, CV disease, cerebrovascular disease, or renal disease
    - History of type 2 diabetes mellitus
    - Depression
    - Symptoms of fibromyalgia
    - Gastroesophageal reflux disease (GERD)

- History of polycystic ovary syndrome
- OSA is most common among males who are 18 to 60 years old, although it is also common at other ages and in women; the prevalence is similar in postmenopausal women and men.

- Untreated OSA has many potential adverse clinical consequences, including EDS, impaired daytime function, metabolic dysfunction, and an increased risk of CV disease and mortality (*Kryger 2020*).
  - The goals of OSA therapy are to resolve signs and symptoms of OSA, improve sleep quality, and normalize the apnea-hypopnea index (AHI) and oxyhemoglobin saturation level.
  - All patients diagnosed with OSA should be offered PAP as initial therapy.
    - CPAP involves maintenance of a positive pharyngeal transmural pressure so that the intraluminal pressure exceeds the surrounding pressure. CPAP also stabilizes the upper airway through increased end expiratory lung volume. As a result, respiratory events due to upper airway collapse (eg, apneas, hypopneas) are prevented.
  - In patients with mild to moderate OSA who prefer not to use PAP or who fail to respond to it, oral appliances are an alternative therapy that have been shown to improve signs and symptoms of OSA and may be better tolerated in some patients than PAP. Upper airway surgery may supersede oral appliances as alternative therapy in patients with severe, surgically correctable, obstructing lesions of the upper airway.
  - Behavior modification is indicated for all patients who have OSA and a modifiable risk factor. Overweight or obese patients should be encouraged to lose weight. Patients with positional OSA should change their sleep position accordingly. All patients should be advised that alcohol and certain common medications, such as benzodiazepines, may worsen their OSA.
  - A variety of pharmacologic agents have been evaluated in RCTs as potential primary therapy for the management of sleep-disordered breathing in OSA, with the goal of replacing more burdensome therapies such as PAP or oral appliances. However, no pharmacologic agent has proven to be sufficiently effective to warrant replacement of such therapies.
  - Residual sleepiness is reported by approximately 10 to 15% of patients with adequately treated OSA (*Pepin 2020*).
    - Modafinil or armodafinil may be beneficial as adjunctive therapy for EDS that persists despite documentation of adequate and successful conventional therapy. The efficacy of these agents, particularly modafinil, for treatment of residual sleepiness in patients with OSA has been demonstrated in multiple RCTs and meta-analyses (*Kryger 2020, Pepin 2020*).

SWD

- Individuals who work night shifts commonly experience difficulties with both sleep and alertness at desired times, and shift work is increasingly recognized as a risk factor for a variety of adverse health outcomes including diabetes, cancer, and CV disease. While some shift workers show circadian adjustment to their work schedule, many others do not (*Cheng & Drake 2019*).
  - Those who do not adjust commonly experience excessive sleepiness during work and significant sleep disturbance. It is estimated that one-third or more of shift workers experience impairments of sufficient severity to meet formal criteria for SWD (ie, development of sleep disturbances and impairment of waking alertness and performance) (*Morgenthaler et al 2007b*).
  - Both sleep duration and sleep quality are commonly affected in shift workers. Shift workers generally report 30 to 60 minutes less sleep compared with day workers, and individuals with SWD report even greater reductions in sleep, with an average decrease of approximately 90 minutes.
  - Shift workers commonly report difficulty with sleep initiation and maintenance. Disturbances during wakefulness include excessive sleepiness, impaired cognitive function, decreased psychomotor functioning, and altered social and emotional functioning.
- Minimum measures to improve sleep after a night shift include a regular sleep schedule (ie, “anchor sleep”), light-blocking shades, and ambient noise control. If family or social responsibilities prohibit one 7- to 9-hour sleep period, a regularized 3- to 4-hour morning "anchor" sleep with a second variably timed sleep period is recommended (*Cheng & Drake 2019*).
- For patients with persistent difficulties obtaining adequate sleep despite sleep hygiene measures, options include use of a short-acting hypnotic agent, exogenous melatonin, and behavioral treatment of insomnia (sleep scheduling and cognitive-behavioral therapy). The choice among these depends on availability and cost, presence of contraindications, and patient preference (*Cheng & Drake 2019*).
  - Modafinil and armodafinil are options in patients with persistent sleepiness in conjunction with nonpharmacologic measures to improve sleep and alertness. The magnitude of benefit may vary among individuals. The observed benefits in RCTs have been modest, however, and AEs may outweigh benefits in some patients.

INDICATIONS

Table 1. FDA-approved indications for narcolepsy agents

Indication	armodafinil	modafinil	pitolisant	sodium oxybate/oxybate salts	solriamfetol
Narcolepsy	√	√	√	√	√
Narcolepsy-cataplexy			√	√	
OSA	√	√			√
SWD	√	√			

- Armodafinil is indicated to improve wakefulness in adult patients with excessive sleepiness associated with narcolepsy, OSA, or SWD.
  - Limitations of Use
    - In OSA, armodafinil is indicated to treat excessive sleepiness and not as treatment for the underlying obstruction. If CPAP is the treatment of choice for a patient, a maximal effort to treat with CPAP for an adequate period of time should be made prior to initiating and during treatment with armodafinil for excessive sleepiness.
- Modafinil is indicated to improve wakefulness in adult patients with excessive sleepiness associated with narcolepsy, OSA, or SWD.
  - Limitations of Use
    - In OSA, modafinil is indicated to treat excessive sleepiness and not as treatment for the underlying obstruction. If CPAP is the treatment of choice for a patient, a maximal effort to treat with CPAP for an adequate period of time should be made prior to initiating and during treatment with modafinil for excessive sleepiness.
- Pitolisant is indicated for the treatment of EDS or cataplexy in adult patients with narcolepsy.
- Sodium oxybate/oxybate salts are indicated for the treatment of cataplexy or EDS in patients ≥ 7 years of age with narcolepsy.
- Solriamfetol is indicated to improve wakefulness in adult patients with EDS associated with narcolepsy or OSA.
  - Limitations of Use
    - Solriamfetol is not indicated to treat the underlying airway obstruction in OSA. Ensure that the underlying airway obstruction is treated (eg, with CPAP) for at least 1 month prior to initiating solriamfetol for EDS. Modalities to treat the underlying airway obstruction should be continued during treatment with solriamfetol. Solriamfetol is not a substitute for these modalities.
- Off-label Uses (*Micromedex 2020; Class IIb or higher recommendation; evidence favors efficacy*) (see Appendix J for description of recommendation, efficacy, and evidence ratings)
  - Armodafinil
    - Bipolar disorder, depressed phase, in combination with conventional medications (Class IIb; Category B)
  - Modafinil
    - Attention deficit hyperactivity disorder (adult and pediatric) (Class IIb, Category B [adult]; Category A [pediatric]
    - Depression, unipolar or bipolar (Class IIb; Category B)
    - Depression; adjunct – fatigue (Class IIb; Category B)
    - Sleep deprivation (Class IIa; Category A)
    - Steinert myotonic dystrophy syndrome (Class IIb; Category B)
  - Sodium oxybate
    - Fibromyalgia (Class IIb; Category B)

PHARMACOLOGY

- Modafinil/armodafinil
  - The mechanism(s) through which armodafinil/modafinil promotes wakefulness is unknown. Armodafinil (R-modafinil) has pharmacological properties similar to those of modafinil (a mixture of R- and S-modafinil), to the extent tested in animal and *in vitro* studies. The R- and S-enantiomers have similar pharmacological actions in animals.
  - Armodafinil and modafinil have wake-promoting actions similar to sympathomimetic agents including amphetamine and methylphenidate, although their pharmacologic profile is not identical to that of the sympathomimetic amines.
  - Modafinil-induced wakefulness can be attenuated by the α1-adrenergic receptor antagonist, prazosin; however, modafinil is inactive in other *in vitro* assay systems known to be responsive to α-adrenergic agonists such as the rat vas deferens preparation.
  - Armodafinil is an indirect dopamine receptor agonist. Modafinil is not a direct- or indirect-acting dopamine receptor agonist. Both armodafinil and modafinil bind *in vitro* to the dopamine transporter and inhibit dopamine reuptake. For modafinil, this activity has been associated *in vivo* with increased extracellular dopamine levels in some brain regions of animals. In genetically engineered mice lacking the dopamine transporter (DAT), modafinil lacked wake-promoting activity, suggesting that this activity was DAT-dependent. However, the wake-promoting effects of modafinil, unlike those of amphetamine, were not antagonized by the dopamine receptor antagonist haloperidol in

rats. In addition, α-methyl-p-tyrosine, a dopamine synthesis inhibitor, blocks the action of amphetamine, but does not block locomotor activity induced by modafinil.
  - In the cat, equal wakefulness-promoting doses of methylphenidate and amphetamine increased neuronal activation throughout the brain. Modafinil at an equivalent wakefulness-promoting dose selectively and prominently increased neuronal activation in more discrete regions of the brain. The relationship of this finding in cats to the effects of modafinil in humans is unknown.
  - In addition to its wake-promoting effects and ability to increase locomotor activity in animals, modafinil produces psychoactive and euphoric effects, alterations in mood, perception, thinking, and feelings typical of other CNS stimulants in humans. Modafinil has reinforcing properties, as evidenced by its self-administration in monkeys previously trained to self-administer cocaine; modafinil was also partially discriminated as stimulant-like.
  - Based on nonclinical studies, 2 major metabolites, acid and sulfone, of modafinil or armodafinil, do not appear to contribute to the CNS-activating properties of the parent compounds.
- Pitolisant:
  - The mechanism of action of pitolisant in EDS in adult patients with narcolepsy is unclear. However, its efficacy could be mediated through its activity as an antagonist/inverse agonist at H_3 receptors.
- Sodium oxybate/oxybate salts
  - Sodium oxybate is a CNS depressant. The mechanism of action of sodium oxybate in the treatment of narcolepsy is unknown. Sodium oxybate is the sodium salt of GHB, an endogenous compound and metabolite of the neurotransmitter GABA. Oxybate salts is a mixture of calcium oxybate, magnesium oxybate, potassium oxybate, and sodium oxybate. It is hypothesized that the therapeutic effects of sodium oxybate and oxybate salts on cataplexy and EDS are mediated through GABA actions at noradrenergic and dopaminergic neurons, as well as at thalamocortical neurons.
- Solriamfetol
  - The mechanism of action of solriamfetol to improve wakefulness in patients with EDS associated with narcolepsy or OSA is unclear. However, its efficacy could be mediated through its activity as a DNRI (*Sunosi prescribing information 2019*). Solriamfetol does not release norepinephrine, differentiating it from the noradrenergic-releasing effects of amphetamines (*Sunosi dossier 2019*).

CLINICAL EFFICACY

STUDY DESIGN ABBREVIATIONS: AC = active control; CI = confidence interval, DB = double-blind; HR = hazard ratio; MC = multi-center; OL = open-label; OR = odds ratio; PC = placebo-controlled; PG = parallel-group; RCT = randomized controlled trial; RR = relative risk; SB = single-blind; SC = single-center; XO = crossover

***Search Strategy**: Studies supporting the FDA-approved indications were identified using search terms "solriamfetol," "armodafinil," "modafinil," "sodium oxybate," "oxybate salts," "pitolisant," "obstructive sleep apnea," "cataplexy," "narcolepsy," and "shift work sleep disorder" through October 14, 2020. Manufacturer submitted data were also reviewed when available. A comprehensive PubMed literature search was performed for human studies published in English. Assessment of each study's design (eg, randomization, blinding methodology, appropriateness of treatment outcomes, etc.), validity and importance was completed. Review of patient data in groups to which they were randomized (intention to treat analysis), accounting for patient withdrawals, and baseline characteristics was completed.*

Modafinil/armodafinil

Narcolepsy

Study 1. Harsh et al, *Curr Med Res Opin.* 2006;22(4):761-774

Study Objective: Evaluate the efficacy and safety of armodafinil for the treatment of EDS in patients with narcolepsy	
Study Design, Follow-up	**Treatment Groups** (N = 196)
• 12-week, Phase 3, DB, PC, PG, MC, RCT	• Armodafinil 150 mg once daily (n = 64) • Armodafinil 250 mg once daily (n = 67) • Placebo (n = 63) • Study medication was administered before 8:00 AM (~30 min before breakfast) throughout the study. • Armodafinil was initiated at a dose of 50 mg/day in all patients; doses were increased to 100 mg/day on day 2 and titrated upward in 50 mg increments every 2 days until the final dose was achieved.
Inclusion Criteria	**Exclusion Criteria**

• Age 18 to 65 years • Diagnosis of narcolepsy according to the International Classification of Sleep Disorders (ICSD) criteria • No medical or psychiatric disorders other than narcolepsy that could have caused EDS • Mean sleep latency ≤ 6 min on the MSLT (Appendix B) and a Clinical Global Impression of Severity (CGI-S) rating ≥ 4 (moderately ill)	• Clinically significant uncontrolled medical or psychiatric illnesses (treated or untreated) • Probable diagnosis of a current sleep disorder other than narcolepsy in the opinion of the investigator • Consumption of > 600 mg/day of caffeine • History of alcohol, narcotic, or other drug abuse • Any disorder that might interfere with drug absorption, distribution, metabolism, or excretion • Use of disallowed drugs (modafinil, melatonin, sodium oxybate, lithium, St. John's Wort, methylphenidate, amphetamines, pemoline, antipsychotic agents, benzodiazepines, zolpidem, MAOIs, anticoagulants, anticonvulsants, barbiturates) • Use of clinically significant amounts of nonprescription drugs within 7 days of the screening visit • Use of anticataplectic drugs (ie, clomipramine, SSRIs, venlafaxine), other than sodium oxybate, were permitted if they did not contribute to patients' sleepiness and if doses were stable for at least 1 month prior to baseline
Co-primary Endpoints	**Secondary Endpoints**
• Change from baseline in mean sleep latency on the MWT 9:00 AM to 3:00 PM (Appendix C) • Proportion of patients with at least minimal improvement on the CGI-C	• Mean changes from baseline in the MWT 3:00 PM to 7:00 PM mean sleep latency • Attention and memory as assessed by the Cognitive Drug Research (CDR) battery (average of first 4 test sessions at 9:30 AM, 11:30 AM, 1:30 PM, and 3:30 PM) • ESS scores (Appendix D) • CGI-C ratings • BFI (score for global fatigue and score for worst fatigue over the previous 24 hours; range 1 to 10; a score ≥ 7 indicates severe fatigue [*Mendoza et al 1999*]) • Data from diaries (sleepiness, mistakes/near misses/accidents, and caffeine use)

- **Results:**
  - At baseline, the placebo and armodafinil 150 mg and 250 mg groups were generally well matched, although patients in the armodafinil 250 mg group were significantly younger than patients in the other groups ($p < 0.05$).
  - At screening, CGI-S ratings were similar across groups, with the majority of patients having marked or severe illness (mean sleep latency < 3 min on the MSLT), and no differences were found between groups in MSLT. In the placebo group, 65% of patients had cataplexy vs 69% and 66% in the armodafinil 150 mg and 250 mg groups, respectively.
  - Study discontinuation rates were 25% (n = 16) in the armodafinil 150 mg group; 16% (n = 11) in the armodafinil 250 mg group; and 14% (n = 9) in the placebo group (18.4% total discontinuation rate).
  - At the final visit, mean MWT 9:00 AM to 3:00 PM sleep latency increased 1.3, 2.6, and 1.9 min from baseline in the 150 mg, 250 mg, and armodafinil combined groups, respectively, and decreased 1.9 min from baseline in the placebo group. Treatment differences from placebo were 3.2, 4.5, and 3.8 min in the 150 mg, 250 mg, and armodafinil combined groups, respectively (all $p < 0.01$).
  - Mean MWT 3:00 PM to 7:00 PM sleep latency at the final visit increased 1.5, 1.6, and 1.6 min in the 150 mg, 250 mg, and armodafinil combined groups, respectively, and decreased 1.2 min from baseline in the placebo group. Treatment differences relative to placebo were 2.7, 2.8, and 2.8 min, for the 150 mg, 250 mg, and armodafinil combined groups, respectively. The differences for the armodafinil combined group vs placebo and the 150 mg group vs placebo were significant ($p < 0.05$ for both comparisons). The armodafinil groups, individually and collectively, also had numerically longer mean MWT 3:00 PM to 7:00 PM sleep latencies when compared with placebo at weeks 4, 8, and 12. These differences did not achieve statistical significance.
  - The proportion of patients with at least minimal improvement in the CGI-C was significantly higher for the armodafinil 150 mg, 250 mg, and combined groups compared with placebo at all time points during the study ($p < 0.0001$ for both individual doses and the combined group vs placebo at final visit). The proportion of patients rated as minimally, much, and very much improved on the CGI-C from baseline to final visit was 21%, 33% and 16%, respectively, for armodafinil 150 mg; 20%, 35%, and 18%, respectively, for armodafinil 250 mg; 20%, 34%, and 17%, respectively, for the armodafinil combined group; and 17%, 12%, and 3%, respectively, for placebo.

- At final visit, power of attention was significantly improved in the armodafinil 150 mg/day and armodafinil combined groups compared with placebo ($p < 0.05$). Although there were numerical differences in favor of both armodafinil dose groups and the combined group compared with placebo at each visit, statistical significance was not observed until the final visit. Effects on mean continuity of attention were numerically improved for the armodafinil groups compared with placebo, but the difference did not achieve statistical significance. At final visit, armodafinil (both doses and the combined group) demonstrated significantly greater improvements in quality of episodic secondary memory relative to placebo ($p < 0.05$). Improvement was observed at the week 4 visit and was maintained throughout the study. Armodafinil 250 mg and the combined group demonstrated significantly greater improvement in speed of memory relative to placebo ($p < 0.05$) at final visit.
- Differences in the change from baseline on the ESS were statistically significant in favor of each armodafinil group compared with placebo at weeks 8 ($p < 0.01$ for all comparisons) and 12 ($p < 0.01$) and at final visit (mean ± SD change from baseline: 150 mg/day, -4.1 ± 5.13, $p = 0.0044$; 250 mg/day, -3.8 ± 4.73, $p = 0.0015$; combined group, -3.9 ± 4.91, $p = 0.0006$). At week 4, there was a statistically significant difference in favor of armodafinil 150 mg/day ($p = 0.0402$). In patients receiving armodafinil 250 mg/day, the difference was not statistically significant ($p = 0.0760$). At the final visit, 21% of patients in the armodafinil 150 mg/day group ($p = 0.0312$) and 28% of patients in the armodafinil 250 mg/day group ($p = 0.0023$) had an ESS score < 10, compared with only 7% of patients in the placebo group.
- Improvements on the BFI in the armodafinil 150 mg/day, 250 mg/day, and combined armodafinil group at final visit were statistically greater than placebo (mean change from baseline: 150 mg/day, -1.5 ± 2.14, $p = 0.0007$; 250 mg/day, -1.3 ± 2.09, $p = 0.0018$; combined group, -1.4 ± 2.11, $p = 0.0002$; placebo, -0.3 ± 1.89). There was a trend toward improvement from baseline in mean worst fatigue scores over the previous 24 hours at final visit, but the differences with armodafinil (all groups) vs placebo were not statistically significant ($p > 0.05$).
- Treatment with armodafinil 150 and 250 mg/day reduced the mean daily number of unintended sleep episodes by 33% and 44%, respectively, compared with a 10% reduction seen in the placebo group ($p < 0.0001$ for overall treatment comparison). The mean number of daily naps was reduced by 41%, 44%, and 22%, respectively, for the armodafinil 150 mg, armodafinil 250 mg, and placebo groups ($p = 0.0039$ for overall treatment comparison). The mean number of mistakes/near misses/accidents was reduced by 43% and 30% in the armodafinil 150 mg/day and 250 mg/day groups, respectively, compared with a 10% reduction in the placebo group. These differences, however, did not achieve statistical significance ($p = 0.1792$ for overall treatment comparison). Caffeine use, which was measured by the number of caffeinated drinks consumed each day, remained similar in the armodafinil and placebo groups (mean change from baseline, -0.7, -1.6, and 0.6 for armodafinil 150 mg, armodafinil 250 mg, and placebo, respectively).
- Headache, nausea, dizziness, and decreased appetite were the most commonly reported AEs. Most were considered mild to moderate, occurred with the greatest frequency during the first 2 weeks of therapy, and were self-limiting.
- There were no significant effects of armodafinil on nighttime sleep, including sleep initiation, continuity, or sleep stage variable as assessed by PSG. There was no change in the incidence of self-reported cataplexy.

- **Authors' conclusion:**
  - In patients with EDS associated with narcolepsy, armodafinil, at doses of 150 or 250 mg/day, significantly improved wakefulness throughout the day, clinician ratings of overall clinical condition, and some measures of memory and attention compared with placebo.
- **Study Appraisal:**
  - **Study sponsorship:**
    - Cephalon
  - **Study rating:**
    - Fair
  - **Study strengths:**
    - Both objective and subjective measures were used to assess efficacy.
  - **Study limitations:**
    - The study was of short duration and did not provide information on the long-term efficacy and safety of armodafinil.
    - The study was not powered to detect differences between the 150 mg and 250 mg armodafinil doses. In addition, there was a significant difference in baseline MWT sleep latency between the 150 mg and 250 mg dose groups. Thus, additional research is needed to clarify the dose proportionality of armodafinil in the narcolepsy population.
    - The effect of armodafinil on memory processes requires further study.

Study 2. Golicki et al, *Med Sci Monit.* 2010;16(8):177-186

Study Objective: Evaluate the efficacy and safety of modafinil vs no active treatment or other drugs in the treatment of narcolepsy

Study Design, Follow-up	Treatment Groups
• Systematic review and meta-analysis (9 RCTs, N = 1054) • Three studies were SC; 4 were MC in 1 country and 2 were MC in more than 1 country. • Sample size varied between 10 and 283; however, only 3 studies included > 100 patients. • All studies were DB and 5 were XO.	• Modafinil any dose or regimen (n = 629) • Placebo or other active treatment (n = 425) • All studies compared modafinil with placebo and 1 also with sodium oxybate in patients with narcolepsy previously treated with modafinil in fixed doses for 4 weeks.
Inclusion Criteria	**Exclusion Criteria**
• Prospective, PG, or XO RCTs, SB or DB published as full text in peer reviewed journals • Study participants with adult (> 17 years old) narcolepsy with or without cataplexy	• Retrospective studies • Studies comparing different doses of modafinil • Secondary publication of an already included study
Primary Endpoints	**Secondary Endpoints**
• Elimination of EDS assessed by objective laboratory tests (MSLT, MWT) or validated subjective outcome measures (ESS) • Number and duration of severe somnolence, sleep attacks and naps, as reported by patients	• QoL assessed by validated generic questionnaires (SF-36) or validated sleep specific questionnaires • Disease severity assessed by the CGI-S • Performance assessed with the 4-choice reaction time test (FCRTT) • Steer Clear Performance Test (SCPT) • Physician evaluation of alerting effect on visual analog scale (VAS) • AEs • Withdrawals due to AEs

- **Results:**
  - Most of the included studies were of good quality and 1 was of poor quality. Five studies did not provide information on allocation concealment, and 4 had adequate allocation concealment. None of the studies reported proper intent-to treat (ITT) analysis; in 2 studies it was unclear and in 3 studies the authors provided analysis for all randomized patients who received study medication and had at least 1 post-baseline measure for efficacy (modified ITT [mITT]). Follow-up ranged from 2 to 9 weeks.
  - A fixed effect model was used by default, but if heterogeneity was detected, a random effects model was used.
  - Modafinil vs placebo:
    - The MSLT was used in 3 studies. In 2 PG studies, there was a greater increase in mean sleep latency with modafinil as compared with placebo: WMD 1.11 min (95% CI, 0.55 to 1.66); I^2 = 0%; test for overall effect: Z = 3.90 (p < 0.0001). The XO study presented median values, which were higher in the modafinil treatment phase compared with the placebo treatment phase (6.6 min vs 3.2 min; p < 0.05).
    - The MWT was used in 6 studies. In 4 PG studies and 2 XO studies, there was a greater increase in mean sleep latency with modafinil as compared with placebo: WMD 2.82 min (95% CI, 2.40 to 3.24); I^2 = 0%; test for overall effect: Z = 13.14 (p < 0.00001). There were similar increases in mean sleep latency in both the PG and XO studies.
    - The ESS scale was used in 6 studies. In 3 PG studies and 1 XO study, there was a greater reduction in the mean ESS score: WMD -2.73 points (95% CI, -3.39 to -2.08); I^2 = 0%; test for overall effect: Z = 8.17 (p < 0.00001). The ESS score was lower with modafinil vs placebo in both the XO and PG studies. In 1 XO study, the median ESS score decreased from 14.5 points during placebo treatment to 12.5 points after 3 weeks of modafinil treatment (p < 0.05). In another PG study which reported median values, no significant change in median average ESS score in the modafinil group was seen as compared with the placebo group (from 14 points to 15 points vs from 16 points to 16 points; p = 0.77).
    - Modafinil also improved the number (p = 0.006) and duration (p = 0.03) of severe somnolence episodes, sleep attacks, and naps per day as compared with placebo.
    - Elimination of cataplexy was assessed in 4 studies. There was no significant effect of modafinil as compared with placebo in 3 XO studies, as well as in 1 PG study: WMD 0.02 (95% CI, -0.27 to 0.31); I^2 = 71%; test for overall effect: Z = 0.13 (p = 0.90).
    - QoL was measured in 2 PG studies using the SF-36 and validated narcolepsy-specific questionnaire. At the end of a 9-week treatment period, patients receiving modafinil compared with those receiving placebo had significantly higher scores in 5 out of 7 narcolepsy-specific domains, SF-36 mental health summary scale and 4 (modafinil 200 mg/day) or 5 (modafinil 400 mg/day) SF-36 domains.

- CGI-S was assessed in 4 studies. In 1 XO study, CGI-S was non-significantly higher during the 4-week modafinil treatment period compared with the placebo phase (2.29 vs 2.0; p = 0.19). Two out of 3 PG studies showed significantly larger numbers of patients who improved according to physician assessment as compared with placebo groups. One study did not show a significant effect. The pooled effect estimate was significant (RR 1.6, 95% CI, 1.32 to 1.95); however, there was moderate heterogeneity (I^2 = 46%), introduced by Black and Houghton 2006 (see study 9 below), which enrolled patients already treated with modafinil and used different doses of the drug. Pooled CGI data from 2 studies showed significant improvement with no corresponding heterogeneity (RR 2.83, 95% CI, 1.90 to 4.20; I^2 = 0%).
- FCRTT was assessed in 3 studies. In 1 XO study, the modafinil treatment phase compared with the placebo treatment phase was associated with significant reductions in the number of gaps and the percentage of errors, and non-significant reduction in the mean reaction time. In another XO study and PG study, no significant difference between the modafinil and placebo groups were observed.
- SPCT was assessed in 2 studies. Significant improvement in driving ability was observed in the modafinil group as compared with the placebo group (WMD -2.54, 95% CI, -4.24 to -0.85).
- Physician evaluation of alerting effect on VAS scale was used in 1 XO study. No significant difference between the modafinil and placebo treatment phase was seen for alerting effect.

○ Modafinil vs sodium oxybate:
- No significant difference was observed between modafinil and sodium oxybate groups in the change of the mean sleep latency as measured by the MWT (MD -1.11 (95% CI, -3.02 to 0.8). The ESS score decreased in sodium oxybate group from 15 to 12 points and increased in modafinil group from 14 to 15 points (see study 9 below).

○ Safety:
- Modafinil was associated with more patient withdrawals from treatment due to AEs (4% vs 1.6% in placebo group); however, pooled RR was not significant: 2.06 (95% CI, 0.83 to 5.09); I^2 = 14%; test for overall effect: Z = 1.57 (p = 0.12).
- Significantly more patients reported nausea in the modafinil group as compared with placebo group. Other reported AE rates were similar between the groups.
- In the study comparing modafinil with sodium oxybate, non-significantly fewer patients in modafinil group compared to sodium oxybate group discontinued treatment due to AEs (3.2% vs 7.3%). Any AE rate was also similar in the modafinil and sodium oxybate groups (54% vs 60%). The most commonly reported AE was nausea, which was rare in the modafinil compared to the sodium oxybate group (3.2% vs 22%; RR 0.15, 95% CI, 0.03 to 0.62). Other AE rates were similar in modafinil and sodium oxybate groups.

• **Authors' conclusion:**
○ On the basis of 9 included studies, it can be concluded that in patients with narcolepsy modafinil in comparison with placebo was associated with significant benefit in terms of elimination of EDS assessed by objective laboratory tests or validated subjective outcome measures, but was not different from placebo in elimination of cataplexy as measured by the number of attacks per day. In addition, modafinil improved QoL of narcolepsy patients measured both by generic and a narcolepsy-specific questionnaire, and was associated with greater likelihood of improvement according to physician assessment.
○ On the basis of 1 study, it can be concluded that modafinil had a similar effect on EDS as sodium oxybate.
○ Modafinil has not been compared directly to methylphenidate, a common treatment of EDS, in any RCTs.

• **Study Appraisal:**
○ **Study sponsorship:**
- The review was partially based on Health Technology Assessment (HTA) report prepared by 2 of the authors to support Polish reimbursement application of modafinil manufactured by Torrex Chiesi. Both authors received grants from Torrex Chiesi Poland Sp.zo.o.

○ **Study rating:**
- N/A

○ **Study strengths:**
- The MA included a large number of RCTs, structured assessment of study quality, and pooled assessment of the modafinil treatment effect.

○ **Study limitations:**
- The length of follow-up of the included studies was short (2 to 9 weeks).
- Due to the small number of trials it was not possible to formally assess the presence of publication bias.
- More than half of the included studies were of XO design. Pooling of XO and PG group studies is considered controversial by some researchers. In this analysis, results of XO and PG studies were pooled separately in subgroups, and then all together.

Study 3. Mitler et al. *Sleep Med.* 2000;1(3):231-243

- A 40-week, OL extension study assessed the long-term efficacy and safety of modafinil in 478 patients with EDS associated with narcolepsy who completed 1 of the 2 pivotal 9-week RCTs of modafinil. A flexible-dose regimen (ie, 200, 300, or 400 mg daily) was followed in 1 study. In the second study, patients received 200 mg/day for 1 week, followed by 400 mg/day for 1 week. Investigators then prescribed either 200 or 400 mg doses for the duration of the study; the majority of patients (~75%) received 400 mg/day. The study was completed by 341 patients (71%).
  - At week 2, CGI-C scores indicated improvement in disease severity in 394/477 (83%) patients from OL baseline which was sustained through week 40. CGI-C scores indicated no change in disease severity in 7 ± 10% of patients and a worsening of symptoms in 9 ± 10% of patients. A total of 236 of 477 patients (49%) were considered much improved or very much improved at week 2. The percentage of patients considered to be much improved or very much improved increased significantly to 58, 59, and 58%, respectively, at weeks 8, 24, and 40 ($p < 0.001$ vs week 2 at all time points). The mean ESS score improved significantly from 16.5 at OL baseline to 12.4 at week 2 and remained at that level through week 40 ($p < 0.001$). QoL scores at weeks 4, 8, 24, and 40 were significantly improved vs OL baseline scores for 6 of the 8 SF-36 domains ($p < 0.001$).
  - The most common treatment-related AEs were headache (13%), nervousness (8%), and nausea (5%). Most AEs were mild to moderate in severity. Forty-three patients (9.0%) discontinued treatment because of AEs.
  - The authors concluded that modafinil was effective for the long-term treatment of EDS associated with narcolepsy and significantly improved perceptions of general health. Modafinil was well tolerated, with no evidence of tolerance developing during 40 weeks of treatment.

Study 4. Black et al. *J Clin Sleep Med.* 2010;6(5):458-66

- The long-term efficacy and safety of armodafinil in patients with EDS associated with treated OSA, SWD, or narcolepsy who completed one of four 12-week pivotal RCTs was assessed in a 12-month, flexible-dose (50 to 250 mg/day), OL extension study. Of 743 enrolled patients (474 with treated OSA, 113 with SWD, and 156 with narcolepsy), 57% of patients (420/743) completed 12 months or more of treatment.
  - Compared with baseline, minimal or greater improvement on the CGI-C was reported by most patients in the 3 diagnostic groups (75 to 92%) at final visit; patients in the SWD group reported the greatest improvement. A rating of much or very much improved was reported at the final visit by 65% (295/457) of patients with treated OSA (95% CI, 60.2 to 68.9), 88% (92/105) with SWD (95% CI, 81.3 to 93.9), and 62% (93/150) with narcolepsy (95% CI, 54.2 to 69.8). At baseline, the proportion of patients with a normal ESS score (ie, < 10) was 0.4% (2/454) in the treated OSA group and 3.4% (5/147) in the narcolepsy group. At the final visit, mean ESS score was reduced by 6.4 (95% CI,
    -6.90 to -5.94) in the treated OSA group and by 4.3 (95% CI, -5.20 to -3.49) in the narcolepsy group. The proportion of patients with an ESS score < 10 at final visit was 54.8% (249/454) for treated OSA and 31.3% (46/147) for narcolepsy. At final visit, mean global BFI scores were reduced by 1.7 (95% CI, -1.88 to -1.43) in the treated OSA group, 2.3 (95% CI, -2.75 to -1.87) in the SWD group, and 1.7 (95% CI, -2.13 to -1.35) in the narcolepsy group; mean worst fatigue scores were reduced by 1.8 (95% CI, -2.13 to -1.57) in the treated OSA group, 2.4 (95% CI, -3.06 to -1.83) in the SWD group, and 1.5 (95% CI, -2.00 to -1.07) in the narcolepsy group.
  - The most commonly reported AEs were headache (25% [180/731]), nasopharyngitis (17% [123/731]), insomnia (14% [99/731]), and upper respiratory tract infection (10% [76/731]). Most AEs were mild or moderate in intensity. Modest increases were observed in vital sign measurements (BP [3.6/2.3 mm Hg], heart rate [6.7 beats per min (bpm)]) across all patient groups; most of the changes occurred by month 3. Discontinuations due to AEs occurred in 13% of patients (95/743) during the 12-month period.
  - The authors concluded that armodafinil remained effective and was generally well tolerated. Increased monitoring of BP may be appropriate in patients on armodafinil. Armodafinil represents an option for long-term treatment of patients with EDS associated with treated OSA, SWD, or narcolepsy.

<u>OSA</u>

Study 5. Kuan et al, *Clin Ther.* 2016;38(4):874-888

Study Objective: Evaluate the efficacy of modafinil and armodafinil in treating EDS in patients with OSA	
Study Design, Follow-up	**Treatment Groups**
• Systematic review and meta-analysis (N = 11 modafinil RCTs and 5 armodafinil RCTs)	• Modafinil 200 to 400 mg daily x 1 to 12 weeks (N = 723) • Armodafinil 150 to 250 mg daily x 2 to 12 weeks (N = 1009) • Placebo • Sample sizes of the 16 RCTs ranged from 20 to 392.
Inclusion Criteria	**Exclusion Criteria**

• RCTs that: ○ Compared the outcomes of the use of placebo and either modafinil or armodafinil in patients with OSA ○ Described all inclusion and exclusion criteria used for patient selection ○ Reported doses and durations of study drugs	• Trials that included patients < 18 years of age or duplicate reports of patient cohorts
Primary Endpoints	**Secondary Endpoints**
• Sleep latency assessed by the MSLT or MWT • ESS • Karolinska Sleepiness Scale (KSS) (Appendix E) • Stanford Sleepiness Scale (SSS) (Appendix F)	• CGI-C • Patient-reported daily function assessed using the 10-item Functional Outcomes of Sleep Questionnaire (FOSQ-10), which measures functional status for disorders of EDS • Psychomotor Vigilance Tests

- **Results:**
  - Most trials investigated whether modafinil or armodafinil with concurrent CPAP use improved sleepiness, neurocognitive performance, and functional outcome in patients with sleep apnea. In 2 studies, CPAP was stopped during modafinil treatment. One study of modafinil and 1 study of armodafinil included untreated patients with OSA. Two studies of modafinil did not specify whether patients received CPAP.
  - Six studies reported acceptable methods of randomization and 6 studies described methods of allocation concealment. All studies reported patient blinding and the outcomes assessors used, and 1 trial reported the blinding of clinicians. Two studies used an ITT analysis without loss to follow-up. For all studies, the acceptable percentage of patients lost to follow-up was < 20%, except in 2 studies in which the levels were 20% and 21%.
  - A pooled estimate of the MDs in sleepiness parameters vs placebo were calculated using a random effects model.
  - Subjective sleepiness:
    - Subjective sleepiness in patients with OSA receiving CPAP was assessed using ESS in 5 RCTs of modafinil and 4 RCTs of armodafinil. Modafinil (WMD -2.95 [95%CI, -3.73 to -2.17]) and armodafinil (WMD -2.78 [95%CI, -3.51 to -2.05]) significantly improved subjective sleepiness compared with placebo ($I^2 = 0\%$).
    - Four studies evaluated the effects of modafinil on subjective sleepiness during acute CPAP withdrawal or in CPAP-naïve patients with OSA. There was a significant reduction in daytime sleepiness duration ($p < 0.05$) and significant improvements on the ESS ($p = 0.003$ [1 study]), KSS ($p = 0.04$ and $p = 0.01$ [2 studies]), SSS ($p = 0.03$ [1 study]), and daytime sleepiness VAS ($p = 0.01$ [1 study]). A non-significant trend of improved self-reported sleepiness on the ESS after armodafinil use among patients with OSA before CPAP treatment was observed in 1 study ($p = 0.066$).
  - Objective sleepiness:
    - Sleep latency with CPAP use was assessed using the MWT after modafinil treatment in 4 studies and after armodafinil treatment in 3 studies. Sleep latency was significantly prolonged in the modafinil group vs the placebo group (WMD 2.51 [95% CI, 1.5 to 3.52]) and armodafinil was associated with significant improvement vs placebo (WMD 2.71 [95% CI, 0.02 to 5.37]). However, a meta-analysis of data from 3 RCTs that compared the effects of modafinil and placebo on sleep latency, as assessed by the MSLT found no significant differences.
  - Overall clinical impression and daily functioning:
    - The proportion of patients with improvement on the CGI-C was evaluated in 3 RCTs of modafinil and 4 RCTs of armodafinil. There was significant improvement in both the modafinil and armodafinil groups vs the placebo group, with pooled RR of 1.94 (95% CI, 1.53 to 2.44) and 1.48 (95 % CI, 1.17 to 1.87), respectively.
    - The FOSQ was used in 4 RCTs that evaluated modafinil. Data were pooled on changes from baseline in total scores from 3 RCTs. In 1 study, the modafinil group showed significant improvement compared with placebo with an MD of 1.28 (95% CI, 0.64 to 1.91). The other 2 trials were not included because of incomplete data. One study found a non-significant trend toward improvement with modafinil in total FOSQ score ($p = 0.093$) and another study reported a non-significant trend in the vigilance subdomain of the FOSQ in the modafinil group ($p = 0.06$). One study reported that armodafinil treatment resulted in significant improvement in the subdomains of general productivity ($p = 0.01$) and social outcome ($p = 0.005$) compared with placebo. However, 2 RCTs conducted in an earlier period yielded divergent results regarding the effects of the medications.
  - Neurocognitive and driving performance:
    - Psychomotor vigilance tests indicated significant reductions in mean reaction time in 3 RCTs. Simulated driving performance was significantly improved in patients with OSA and acute CPAP withdrawal ($p = 0.018$) and in those awaiting CPAP initiation ($p < 0.0001$). One study reported a significant improvement in the composite Driving Safety Score ($p = 0.03$), assessed using the Cognitive Research Corporation Driving Simulator, in CPAP-naïve patients with OSA who received armodafinil compared with placebo.
  - AEs:

- Headache was the most commonly reported AE with both medications with RR of 1.78 (95% CI, 1.20 to 2.65) in the modafinil group and 2.04 (95% CI, 1.36 to 3.05) in the armodafinil group. Most AEs were generally of mild to moderate severity. Other AEs included nausea, anxiety or nervousness, insomnia, and dizziness.

- **Authors' conclusion:**
  - Modafinil or armodafinil treatment significantly improved sleepiness, clinical global impression, and total FOSQ scores in patients with OSA and excessive sleepiness with or without concurrent CPAP use. The results on neurocognitive performance were inconsistent. Most AEs were well tolerated.
- **Study Appraisal:**
  - **Study sponsorship:**
    - No funding was received from any industry or organization.
  - **Study rating:**
    - N/A
  - **Study strengths:**
    - Eligibility criteria were applied systematically and explicitly.
  - **Study limitations:**
    - The sample size of some of the included RCTs was small.
    - Most of the trials were short-term, with a maximum duration of 12 weeks.
    - Some numeric data analyzed statistically were estimated using graphics in the original publications because complete data were unavailable.
    - Concurrent use of CPAP was not consistent across all trials.
    - Patients were normotensive at baseline; thus, the study findings cannot be extrapolated to hypertensive patients.

SWD

Study 6. Czeisler et al. *Mayo Clin Proc*. 2009;84:958-972.

Study Objective: Evaluate the effect of armodafinil on the physiologic propensity for sleep and cognitive performance during usual night shift hours in patients with excessive sleepiness associated with chronic moderate to severe SWD	
Study Design, Follow-up	**Treatment Groups** (N = 254)
• 12-week, Phase 3, DB, PC, PG, MC, RCT • Patients were evaluated at weeks 4, 8, and 12 during an overnight laboratory night shift scheduled immediately after a sequence of ≥ 3 consecutive work night shifts.	• Armodafinil 150 mg 30 to 60 minutes before each night shift and no later than 11:00 PM (n = 127) • Placebo (n = 127) • Patients received a dose of 50 mg on the first night, 100 mg on the second and third nights, and 150 mg on all subsequent nights. Patients took study medication only on nights when they worked the night shift or attended the sleep laboratory.
Inclusion Criteria	**Exclusion Criteria**
• Age 18 to 65 years • Worked 5 or more night shifts per month (each shift ≤ 12 hours, with ≥ 6 hours worked between 10:00 PM and 8:00 AM and with ≥ 3 shifts occurring on consecutive nights) and planned to maintain this schedule for the duration of the treatment • Diagnosis of SWD according to the ICSD • SWD of moderate or greater severity, as documented by a CGI-S rating ≥ 4 for sleepiness on work nights, including the commute to and from work • Chronic (≥ 3 months) excessive sleepiness during night shifts, which was corroborated by a mean sleep latency of 6 minutes or less on a nighttime MSLT • Insomnia, as indicated by daytime sleep efficiency of 87.5% or less (determined by 8-hour PSG)	• History of substance abuse or medical or psychiatric disorders that could account for excessive sleepiness during the night shift • Any disorder that might interfere with drug PK • Known sensitivity to stimulants or modafinil • Consumption of an average of > 600 mg/day of caffeine during the 7 days preceding the baseline visit • Use of prescription drugs disallowed by the protocol or clinically important amounts of nonprescription drugs within 7 days of the screening visit
Primary Endpoints	**Secondary Endpoint**
• Change from baseline to final visit (12-week or last post-baseline measurement) in overall mean sleep	• Patient sleepiness assessed using the KSS

latency (averaged across the last 4 nighttime sessions at 2:00, 4:00, 6:00, and 8:00 AM) as assessed by the MSLT • Proportion of patients with at least minimal improvement in the CGI-C during the night shift and commute to and from work at the final visit (12-week or last post-baseline measurement)	• The CDR was administered at 12:30, 2:30, 4:30, 6:30, and 8:30 AM of each laboratory night shift. ○ The CDR battery included tests of memory (eg, numeric working memory test, word recognition test, immediate word recall test, delayed word recall test, and picture recognition test) and attention ○ Composite factors derived from the CDR included quality of episodic secondary memory (ability to encode, store, and retrieve verbal and pictorial information of an episodic nature), speed of memory (time required to retrieve information from episodic and working memory), power of attention (ability to focus attention), and continuity of attention (ability to sustain attention).

- **Results:**
  - Of the 254 patients randomized, 245 (96%) received at least 1 dose of study drug and 172 patients completed the study (84 placebo, 93 armodafinil).
  - The armodafinil and placebo groups were similar in baseline demographic variables and illness severity ratings. Overall, 138 (56%) of 245 patients were rated by the investigator as moderately ill, and 107 (44%) of 245 patients were rated as markedly, severely, or extremely ill. Most patients (212/245; 87%) were permanent night shift workers.
  - Sixty-eight (28%) of 245 patients withdrew from the study (30 in the armodafinil group and 38 in the placebo group). Reasons for discontinuing were AEs (7 in the armodafinil group and 4 in the placebo group), consent withdrawn (3 in the armodafinil group and 16 in the placebo group), loss to follow-up (3 in the armodafinil group and 5 in the placebo group), nonadherence with study procedures (6 in the armodafinil group and 2 in the placebo group), and other (11 in the armodafinil group and 11 in the placebo group). No patients discontinued participation because of lack of efficacy.
  - Patients were severely sleepy at baseline, with mean (SD) sleep latencies on the MSLT of 2.3 (1.6) min for the armodafinil group and 2.4 (1.6) min for the placebo group. The mean KSS score was 7.4 (1.4) in the armodafinil group and 7.3 (1.3) in the placebo group and 97 (87%) of 112 patients in the armodafinil group and 87 (84%) of 104 in the placebo group had a KSS score ≥ 6.
  - Armodafinil significantly improved mean (SD) sleep latency from 2.3 (1.6) min at baseline to 5.3 (5.0) min at final visit, compared with a change from 2.4 (1.6) min to 2.8 (2.9) min in the placebo group ($p < 0.001$).
  - Of 112 armodafinil patients, 89 (79%) were rated as improved on the CGI-C at the final visit compared with 61 (59%) of the 104 placebo patients ($p = 0.001$).
  - The sleep latency for individual MSLT sessions at all 5 time points (midnight to 8:00 AM) at the final visit was greater for patients who received armodafinil than for patients who received placebo ($p < 0.001$ at midnight, 2:00 AM, 4:00 AM; $p = 0.007$ at 6:00 AM; $p = 0.02$ at 8:00 AM).
  - For the armodafinil group, 64 (57%) of 112 patients were very much improved or much improved at the final visit compared with 37 (36%) of 104 patients in the placebo group ($p = 0.002$). The proportion of patients with at least minimal improvement on the CGI-C of sleepiness was significantly greater for armodafinil than for placebo at the 4-week (armodafinil, 89/110 patients [81%]; placebo, 59/100 [59%]; $p < 0.001$), 8-week (armodafinil, 77/99 [78%]; placebo, 45/93 [48%]; $p < 0.001$), and 12-week (armodafinil, 75/96 [78%]; placebo, 50/89 [56%]; $p = 0.001$) assessments.
  - Patient-reported levels of sleepiness during the night shift on the KSS were significantly reduced for the armodafinil group compared with the placebo group at all visits ($p \leq 0.001$ at week 4 and 8; $p \leq 0.01$ at week 12, results shown in graphical form).
  - At the final visit, armodafinil was associated with significant improvement in most items assessed in the electronic diaries, including maximum level of sleepiness during the night shift and commute home and the mean number of mistakes, accidents, or near misses compared with placebo (Table 2).

Table 2. Changes in ratings of sleepiness on the electronic diaries

Characteristic	Placebo (n = 104)			Armodafinil (n = 112)			p-value[c]
	No. of pts[a]	Baseline[b]	Δ from baseline[b]	No. of pts[a]	Baseline[b]	Δ from baseline[b]	
During night shift							

Unintended sleep episodes	88	1.1 (1.0)	-42%	92	1.2 (2.6)	-72%	< 0.001
Intended sleep episodes	79	0.6 (0.6)	-13%	85	0.7 (1.6)	-36%	0.01
Maximum level of sleepiness	99	7.5 (1.0)	-1.1 (1.0)	109	7.5 (1.1)	-2.0 (1.1)	< 0.001
Level of sleepiness during commute home	99	5.9 (1.4)	-0.6 (1.0)	109	5.9 (1.7)	-1.2 (1.2)	0.003
No. of mistakes, near misses, or accidents							
During night shift	66	0.8 (1.0)	-46%	84	1.2 (3.4)	-64%	0.04
During commute home	50	0.3 (0.6)	-47%	60	0.3 (0.4)	-66%	0.12
No. of caffeinated drinks/day	99	1.8 (3.9)	0.0 (1.4)	109	1.3 (1.2)	-0.4 (0.7)	

a Patient numbers represent data from those for whom baseline and post-baseline data were available to calculate change from baseline.
b Values are mean (SD) or percentage.
c Values are based on change from baseline compared with placebo.

- Armodafinil significantly improved standardized memory assessments ($p < 0.001$), mean power of attention ($p = 0.001$), and continuity of attention ($p < 0.001$).
- AEs reported by ≥ 5% of armodafinil patients and more frequently than placebo were headache (15/123 [12%] in the armodafinil group and 12/122 [10%] in the placebo group), nausea (9/123 [7%] in the armodafinil group and 4/122 [3%] in the placebo group), nasopharyngitis (7/123 [6%] in the armodafinil group and 4/122 [3%] in the placebo group), and anxiety (6/123 [5%] in the armodafinil group and 2/122 [2%] in the placebo group). Most AEs were considered mild or moderate.
- Armodafinil did not adversely affect daytime sleep variables (eg, sleep latency, sleep duration, and sleep-stage distribution) compared with placebo.

- **Authors' conclusion:**
  - In patients with excessive sleepiness associated with chronic SWD of moderate or greater severity, armodafinil significantly improved wakefulness during scheduled night work, raising mean nighttime sleep latency above the level considered to indicate severe sleepiness during the daytime. Armodafinil also significantly improved measures of overall clinical condition, long-term memory, and attention.
- **Study Appraisal:**
  - **Study sponsorship:**
    - Cephalon
  - **Study rating:**
    - Fair
  - **Study strengths:**
    - Both objective and subjective measures were used to assess efficacy.
  - **Study limitations:**
    - The study was of short duration and did not provide information on long-term efficacy and safety.
    - There is no validated measure for assessing excessive sleepiness in SWD. Although the MSLT is sensitive to changes in sleepiness during nighttime hours and is recommended for assessing sleepiness at night in this population, it has not been specifically validated as a clinical instrument for measuring nighttime sleepiness.
    - The study did not provide assessments of actual work performance or safety.
    - Most patients enrolled were permanent night shift workers. This may limit the generalizability of these results to individuals working alternative shift schedules.
    - This study was performed in SWD patients with both excessive sleepiness and insomnia, who may represent a more severely affected group; therefore, additional studies may be necessary to quantify the effects in a patient population with less severe SWD.
    - The study did not include patients with SWD associated with starting work in the early morning.

Study 7. Czeisler et al. *N Engl J Med*. 2005;353:476-486.

Study Objective: Evaluate the efficacy and safety of modafinil for the treatment of sleepiness in patients with SWD	
Study Design, Follow-up	**Treatment Groups** (N = 209)
• 3-mo, Phase 3, DB, PC, PG, MC, RCT • Patients were evaluated monthly during an overnight laboratory shift after having worked for 3 or more consecutive nights.	• Modafinil 200 mg 30 to 60 minutes before each night shift (n = 99) • Placebo (n = 110)
Inclusion Criteria	**Exclusion Criteria**

• Age 18 to 60 years • Worked each month ≥ 5 night shifts for ≤ 12 hours, with ≥ 6 hours worked between 10:00 PM. and 8:00 AM and ≥ 3 shifts occurring consecutively. • Diagnosis of SWD according to the ICSD • Chronic excessive sleepiness (≥ 3 months) during night shifts • CGI-S rating of moderately ill or worse for sleepiness on work nights, including the commute home from work; an average latency to sleep onset of ≤ 6 during 20-minute nap opportunities at 2-hour intervals during the night, as measured by the MSLT; and a sleep efficiency of ≤ 87.5% as determined by daytime PSG	• Diagnosis by history and/or diagnostic PSG of a concurrent sleep disorder other than chronic SWD • Presence of clinically significant, uncontrolled psychiatric or medical conditions • Abuse of alcohol, narcotics, or other drugs • Caffeine consumption averaging > 600 mg per day within 1 week of baseline • Use of protocol-prohibited prescription medications (eg, any medication that could make a patient feel sleepy, or clinically significant use of over-the-counter [OTC] drugs within 2 weeks of baseline)
Primary Endpoints	**Secondary Endpoints**
• Rating on the CGI-C test for sleepiness during the night shift, including the commute to and from work, at the final visit • Change between baseline and the final visit (ie, at the third month or at withdrawal from the study) in overall mean sleep latency on the basis of results of the nighttime MSLT	• Patient sleepiness assessed using the KSS • Frequency and duration of lapses of attention during performance on the Psychomotor Vigilance Test ○ This endpoint served as a validated and objective measure of alertness at night

- **Results:**
  - Of 209 patients randomized, 204 patients received the drug and153 patients completed the study (placebo, 81; modafinil 72).
  - At baseline, there were no significant differences in demographic variables, shift-work type, sleepiness, performance, and results on PSG between the group that received modafinil and the one that received placebo.
  - Patients were severely sleepy at baseline, with overall mean (±SD) sleep latencies of 2.0 ± 1.8 minutes and 2.1 ± 1.5 minutes for the placebo and modafinil groups, respectively.
  - Seventy-four percent of patients in the modafinil group were rated as at least minimally improved on the CGI-C test at the final visit, as compared with 36% in the placebo group ($p < 0.001$) (Table 3).
  - Overall mean (± standard error of the mean [SEM]) sleep latency, as measured by the MSLT, increased from 2.1 min at baseline to 3.8 min at the final visit with modafinil (change, 1.7 ± 0.4 min; $p < 0.001$) but not with placebo (2.04 at baseline vs 2.37 at the final visit; change, 0.3 ± 0.3; $p = 0.24$). Sleep latency was significantly greater in the modafinil group than in the placebo group ($p = 0.002$). This improvement in sleep latency with modafinil vs placebo was found at 2:00 AM ($p = 0.02$) and 4:00 AM ($p < 0.001$), but not at 6:00 AM ($p = 0.45$) or 8:00 AM ($p = 0.17$).

Table 3. CGI-C at final visit

CGI-C rating	Number (%) of patients	
	Placebo (n = 104)	Modafinil (n = 89)
Very much improved	8 (8)	21 (24)
Much improved	13 (13)	28 (31)
Minimally improved	16 (15)	17 (19)
No change	61 (59)	20 (22)
Minimally worse	4 (4)	2 (2)
Much worse	2 (2)	1 (1)
Very much worse	0 (0)	0 (0)
p-value		< 0.001

  - Differences between modafinil and placebo in the Psychomotor Vigilance Test were statistically significant.
    - The median number of lapses of attention in 20-minute tests during the night was 12.50 at baseline and 10.25 at the final visit for the modafinil group (median change from baseline, -2.6; $p = 0.012$). In the placebo group, the median number of lapses per test bout was 16.13 at baseline and 23.75 at the final visit (median change from baseline, 3.8; $p = 0.008$). The groups did not differ significantly at baseline ($p = 0.797$), but they did differ significantly at the final visit ($p = 0.005$), and the change in lapses of attention during performance of the Psychomotor Vigilance Test from baseline to the final visit was significant for modafinil vs placebo ($p < 0.001$).

- The duration of lapses showed a similar result, decreasing from baseline (780 msec) to the final visit (669 msec) for patients receiving modafinil and increasing from baseline (852 msec) to the final visit (1235 msec) for those receiving placebo; This resulted in a significant difference at the final visit (p = 0.004) and in the change from baseline to the final visit in favor of modafinil vs placebo (p = 0.019).
- Sleepiness levels on the KSS were also significantly reduced for patients receiving modafinil (baseline mean, 7.3; final visit mean, 5.8; change, -1.5 ± 0.2), as compared with placebo (baseline, 7.1; final visit, 6.7; change, -0.4 ± 0.2) (p < 0.001).

○ As compared with placebo, modafinil reduced the maximum level of sleepiness during the night-shift (p < 0.001 for the change from baseline vs placebo) and the level of sleepiness during the commute home (p = 0.01), and 25% fewer patients receiving modafinil reported having had accidents or near accidents during the commute home (p < 0.001). Modafinil treatment during night shifts had no statistically significant effects on unintentional or intentional sleep episodes, mistakes, accidents or near accidents, or caffeine consumption (Table 4).

Table 4. Variables derived from patient diaries

Variable	Placebo (n = 108)			Modafinil (n = 96)			p-value
	Baseline	After baseline	Change	Baseline	After baseline	Change	
During night shift							
Maximum level of sleepiness — score†	7.4±1.0	6.6±1.3	-0.9±1.0	7.3±0.9	5.4±1.5	-1.9±1.4	< 0.001
No. of unintentional sleep episodes†	1.2±1.3	0.6±0.7	-0.6±1.0	1.0±1.1	0.2±0.4	-0.8±0.9	0.20
No. of intentional sleep episodes†	0.5±0.8	0.4±0.5	-0.1±0.5	0.4±0.5	0.2±0.4	-0.2±0.4	0.13
No. of caffeinated drinks consumed†	1.3±1.1	1.1±0.9		1.3±1.2	1.0±1.0		0.10
Patients reporting mistakes, accidents, or near accidents — no. (%)§		59 (55)			46 (48)		0.34
During commute home							
Level of sleepiness — score†	5.9±1.8	5.4±1.7	-0.6±1.2	5.5±1.8	4.4±1.6	-1.1±1.5	0.012
Patients reporting unintentional sleep episodes — no. (%)§		47 (44)			34 (35)		0.24
Patients reporting accidents or near accidents — no. (%)§		58 (54)			28 (29)		< 0.001¶
During days after night shift							
No, of caffeinated drinks consumed‡**	1.0±1.3	0.6±0.7	-0.4±1.0	0.9±1.1	0.7±0.8	-0.2±1.0	0.61
Sleep efficiency — %**††	78.0±20.7	87.5±14.1	9.5±18.3	80.3±19.9	87.5 ±14.4	7.3±18.5	0.55

* Plus–minus values are means ±SD. Patients recorded responses in electronic diaries on actual work nights. Sleepiness scores were obtained with the use of the KSS. Analysis includes patients with baseline values and values after baseline. For each patient, baseline values and values after baseline are average values calculated before and after the start of DB treatment.
† Data were available for 84 patients receiving placebo and for 79 patients receiving modafinil.
‡ p-value is for the change from baseline for modafinil vs placebo.
§ Values are for the number of patients with a value after baseline. Patients were counted once.
¶ p-value is for modafinil vs placebo.
‡ Data were available for 85 patients receiving placebo and for 78 patients receiving modafinil.
** The time interval was from the end of the night shift until 60 minutes after waking up from the last sleep episode.
†† Data were available for 84 patients receiving placebo and for 78 patients receiving modafinil. Sleep efficiency was calculated as the sleep duration divided by the time spent in bed multiplied by 100 so that scores could range from 0 to 100%.

○ During days following night off, there were no significant differences in caffeine use and sleep efficiency between the modafinil and placebo group.
○ There were no significant differences between modafinil and placebo with respect to any measurement of daytime sleep, including sleep duration, latency, and efficiency, and the proportion and distribution of sleep stages.
○ The use of prescription or nonprescription sleeping pills was not specifically monitored, although concomitant use of medications was queried. Of the 96 patients in the modafinil group, 1 reported use of a prescription hypnotic vs none of the 108 placebo patients. Five of the 96 modafinil patients reported use of OTC sleep aids vs 1 of the 108 placebo patients (p = 0.102).
○ Headache was the most common AE reported in both treatment groups.
○ More patients in the modafinil group than in the placebo group had insomnia (6 vs 0%, respectively; p = 0.01).

- **Authors' conclusion:**
  ○ Treatment with 200 mg of modafinil reduced the extreme sleepiness in patients with SWD and resulted in a small but significant improvement in performance as compared with placebo. However, the residual sleepiness that was observed in the treated patients underscores the need for the development of interventions that are even more effective.

- **Study Appraisal:**
  - **Study sponsorship:**
    - Cephalon
  - **Study rating:**
    - Fair
  - **Study strengths:**
    - Both objective and subjective measures were used to assess efficacy.
  - **Study limitations:**
    - The study was of short duration and did not provide information on long-term efficacy and safety.
    - There is no validated measure for assessing excessive sleepiness in SWD. Although the MSLT is sensitive to changes in sleepiness during nighttime hours and is recommended for assessing sleepiness at night in this population, it has not been specifically validated as a clinical instrument for measuring nighttime sleepiness.
    - The study did not provide assessments of actual work performance.
    - The vast majority of participants were permanent night shift workers; thus, the study findings are not generalizable to other types of shifts that include nighttime hours.

Pitolisant

Study 8. Dauvilliers et al, *Lancet Neurol.* 2013;12:1068-1075 (HARMONY 1)

Study Objective: Evaluate the safety and efficacy of pitolisant in patients with EDS in narcolepsy	
Study Design, Follow-up	**Treatment Groups** (N = 95)
• Phase 3, AC, DB, double-dummy, PC, PG, MC, RCT • The study was conducted in 32 sleep disorder centers in 5 European countries	• Pitolisant (n = 32) • Modafinil (n = 33) • Placebo (n = 30) • Treatment duration was 8 weeks: 3 weeks of flexible dosing followed by 5 weeks of stable dosing ○ Patients took a low dose of study drug (pitolisant 10 mg or modafinil 100 mg or placebo) during the first 7 days, then a medium dose (pitolisant 20 mg or modafinil 200 mg or placebo) for the next 7 days. ○ On day 14, doses were adjusted on the basis of individual clinical efficacy and safety; no specific recommendations were provided to investigators for dose adjustment. ○ Patients could then receive 10, 20, or 40 mg of pitolisant or 100, 200, or 400 mg of modafinil or placebo. ○ On day 21, investigators could decrease the dose in the case of insufficient tolerance only. ○ Patients continued at their assigned stable dose for an additional 5 weeks. ○ On day 49, patients made a control visit, and treatment was stopped at day 56. Patients then received 1 week of placebo in a withdrawal phase. • Within the pitolisant group, the maximum dose of 40 mg was reached by 61% of patients. • Note: Doses are expressed in terms of the salt form: 5, 10, 20, and 40 mg are equivalent to 4.45, 8.9, 17.8, and 35.6 mg (*Wakix FDA clinical review 2019*).
Inclusion Criteria	**Exclusion Criteria**
• Age ≥ 18 years • Diagnosis of narcolepsy with or without cataplexy and self-reported daily EDS for ≥ 3 months Diagnosis was confirmed by PSG, an MSLT performed within the previous 5 years showing a	• Patients could not have psychostimulants for 14 or more days before baseline but could remain on their anticataplectic drugs (sodium oxybate or antidepressants) at stable doses 1 month before and throughout the trial. • Use of TCAs

mean sleep latency ≤ 8 min with ≥ 2 REM periods, and an ESS score ≥ 14	• Another disorder that could be the main cause of EDS in patients without cataplexy (eg, sleep-related breathing disorder with sleep apnea index ≥ 10 per hr or apnea or hypopnea index of ≥ 15 per hr, or a periodic limb movement (PLM) disorder with arousal index of ≥ 10) • History of substance abuse • Serious CV disorder • Hepatic or renal abnormalities • Psychiatric disorder
Primary Endpoint	**Secondary Endpoints**
• The difference in change in ESS scores between the pitolisant and placebo groups after the 8-week treatment period	• MWT • SART (Appendix G) • CGI-C targeting EDS and cataplexy • EQ-5D (defines health using 5 dimensions: Mobility, Self-Care, Usual Activities, Pain/Discomfort, and Anxiety/Depression; overall health is rated on 100-point visual analogue scale [VAS]) (*Herdman et al 2011*) • Patient's global opinion (PGO) of their treatment • Symptoms of cataplexy assessed by patients' sleep diaries（symptoms recorded were sleep attacks, episodes of severe sleepiness, cataplexy attacks, hypnagogic or hypnopompic hallucinations, sleep paralysis, nocturnal awakening, and nocturnal sleep time) • Post-hoc analyses included: ○ Daily cataplexy rate defined as ≥ 1 cataplexy episode during baseline or study treatment period. ○ ESS responder rates defined as patients with a final ESS of ≤ 10

- **Results:**
  - ○ Patients who had at least 1 dose of study drug and provided at least 1 post-baseline value were included in the ITT population.
  - ○ Most of the baseline characteristics were similar among groups. Of the 94 patients included in the ITT analysis, 76 (81%) had a history of cataplexy, 42 (45%) had taken psychostimulants (mostly modafinil or methylphenidate; 13 of 30 patients in the placebo group, 13 of 31 in the pitolisant group, and 11 of 33 in the modafinil group), and 33 (35%) were using anticataplectic drugs and continued them at stable dosage during the trial; of those using anticataplectic drugs, 8 (4 in the placebo group, 2 in the pitolisant group, and 2 in the modafinil group) were on sodium oxybate and 25 used antidepressants. At baseline, the mean daily cataplexy rate was 0.92 in the placebo group, 1.2 in the pitolisant group, and 1.1 in the modafinil group. Fifty-seven (61%) patients were considered still cataplectic during the trial and reported ≥ 1 cataplexy episodes during the trial. The duration of narcolepsy ranged from 10.6 to 14.9 years. The per-protocol (PP) population comprised 79 patients who completed the study: 25 in the placebo group, 26 in the pitolisant group, and 28 in modafinil group.
  - ○ A step-down approach was used for multiple treatment comparisons: superiority of pitolisant over placebo was tested first, then, if shown to be superior, the non-inferiority of pitolisant vs modafinil was tested based on a non-inferiority margin of 2 ESS points.
  - ○ In the ITT analysis, patients in the pitolisant group had a significantly greater improvement from baseline in ESS scores compared with the placebo group (Table 5).
    - ▪ Because the superiority criterion of pitolisant over placebo was met, the non-inferiority of pitolisant to modafinil was tested; the results showed that pitolisant was not non-inferior to modafinil (Table 5).
  - ○ During the trial, ESS decreased at a similar rate in the pitolisant and modafinil groups (data shown graphically). There were no statistically significant between-group differences in analysis of all randomly allocated patients and the PP population (data not shown).
  - ○ MWT values decreased from baseline in the placebo group but improved in the pitolisant group, demonstrating superiority of pitolisant. MWT also improved from baseline in the modafinil group. There was no statistically significant difference between pitolisant and modafinil (Table 5).
  - ○ NO GO error scores in the SART were similar between baseline and end of treatment in the placebo group, whereas they decreased in the pitolisant group, with a statistically significant difference between groups (Table 5).

Changes in the modafinil and pitolisant groups, however, were not statistically different. There were no differences in changes from baseline between either pitolisant and placebo or pitolisant and modafinil in either the SART GO scores or total SART scores (Table 5).

- The proportion of patients who had improvements in EDS assessed by the CGI-C by the end of treatment was largest in the modafinil group and smallest in the placebo group (Table 5). There were little between-group differences in change in severity of cataplexy assessed by the CGI-C.
- EQ-5D values were similar in all 3 groups, whereas PGO on treatment improved only slightly more for pitolisant or modafinil than for placebo (Table 5). The differences were not statistically significant (*Wakix FDA clinical review 2019*).
- The small number of occurrences of other parameters collected in the sleep diaries (hallucinations, sleep attacks, and severe sleepiness) precluded any formal comparison between groups.
- In post-hoc analyses, pitolisant was superior to placebo but not non-inferior to modafinil in terms of improvement in daily cataplexy rate from baseline (Table 5). The percentage reduction in cataplexy rate from baseline to Week 8 was -65% in the pitolisant group, -35% in the modafinil group, and -9% in the placebo group. In other post-hoc analyses, the percentage of responders (with final ESS scores ≤ 10) also differed between the pitolisant and placebo groups and were similar between pitolisant and modafinil (Table 5).

Table 5. Primary and secondary endpoint efficacy results (ITT population)

Endpoint	Placebo		Pitolisant		Modafinil		Treatment difference (MD [95% CI]; p-value)	
	Baseline/final	Δ over trial*	Baseline/final	Δ over trial*	Baseline/final	Δ over trial*	Pitolisant vs placebo (superiority test)	Pitolisant vs modafinil (NI test)
ESS (Δ = final – baseline)	18.9 (2.5)/ 15.6 (4.3)	-3.4 (4.2)	17.8 (2.5/ 12.0 (6.2)	-5.8 (6.2)	18.5 (2.7)/ 11.6 (6.0)	-6.9 (6.2)	-3.0 (-5.6 to -0.4) p = 0.024	0.12 (-2.5 to 2.7); p = 0.250
MWT	8.4 (1.8)/ 7.6 (3.0)	0.88	7.4 (2.3)/ 9.7 (2.8)	1.32	8.8 (2.5)/ 15.1 (2.7)	1.72	1.47 (1.01 to 2.14); p = 0.044	0.77 (0.52 to 1.13); p = 0.173
SART NO GO	8.0 (1.8)/ 8.1 (1.8)	1.0	9.2 (2.0)/ 7.5 (1.9)	0.82	8.5 (2.0)/ 7.1 (1.9)	0.84	0.81 (0.67 to 0.99); p = 0.038	0.97 (0.81 to 1.17); p = 0.765
SART GO	3.5 (0.7)/ 2.7 (0.7)	0.76	3.5 (1.1)/ 2.1 (0.6)	0.6	3.2 (0.7)/ 2.5 (0.6)	0.79	0.79 (0.56 to 1.12); p = 0.176	0.77 (0.54 to 1.20); p = 0.141
SART total	11.5 (2.1)/ 11.4 (2.1)	1.0	12.5 (2.1)/ 10.0 (2.2)	0.8	11.6 (2.1)/ 10.4 (2.2)	0.89	0.80 (0.64 to 1.00); p = 0.053	0.90 (0.71 to 1.14); p = 0.370
CGI-C EDS improved (n/N[%])	--	14/25 (56%)	--	19/26 (73%)	--	24/28 (86%)	--	--
CGI-C cataplexy improved (n/N[%])	--	6/25 (24%)	--	9/26 (35%)	--	8/28 (29%)	--	--
EQ-5D	64 (19.2)/ 70.2 (17.7)	--	65.3 (21.3)/ 73.8 (17.8)	--	58.7 (19.4)/ 72.6 (16.5)	--	--	--
PGO improved (n/N[%])	--	14/25 (56%)	--	24/28 (81%)	--	24/28 (86%)	--	--
ESS responder (post-hoc analysis) (n/N[%])	--	4/30 (13%)	--	14/31 (45%)	--	15/33 (46%)	4.4 (2.1 to 9.2); p < 0.0006	1.0 (0.68 to 1.6); p = 0.908
Cataplexy rate (post-hoc analysis)	0.43 (0.7)/ 0.39 (0.6)	0.92	0.52 (0.6)/ 0.18 (0.4)	0.38	0.4 (0.6)/ 0.26 (0.5)	0.64	0.38 (0.16 to 0.93); p = 0.034	0.54 (0.24 to 1.23); p = 0.138

Abbreviation: NI = non-inferiority
Data are mean (geometric mean) unless otherwise stated
*= change calculated as final-baseline, unless otherwise stated

- The most frequent AEs were headache for the 3 groups, insomnia, abdominal discomfort, and nausea for pitolisant, and abdominal discomfort, nausea, diarrhea, dizziness, anxiety, and irritability for modafinil. There were no clinically relevant between group differences in terms of intensity or resolution of AEs across the 3 groups. Nine AEs reported as severe occurred during the treatment period, of which 6 were deemed treatment-related: 1 with pitolisant (abdominal discomfort) and 5 with modafinil (abdominal pain, abnormal behavior, amphetamine-like withdrawal symptoms, lymphadenopathy, and inner ear disorders).
- No patient receiving placebo or pitolisant experienced a Diagnostic and Statistical Manual of Mental Disorders (DSM)-5-defined withdrawal syndrome during the withdrawal phase compared with 3 patients in the modafinil group.

- **Authors' conclusion:**

- EDS can be improved by pitolisant for at least 2 months, as judged by 2 objective tests in addition to the ESS; pitolisant might also have some anticataplectic activity. Whereas the wake-promoting activity of pitolisant does not differ from that of modafinil, it seems to be better tolerated.

- **Study Appraisal:**
  - **Study sponsorship:**
    - Bioprojet, France (Bioprojet Pharma was acquired by Harmony Biosciences in 2017)
  - **Study rating:**
    - Fair
  - **Study strengths:**
    - Pitolisant was tested for superiority to placebo first; if shown to be superior, the non-inferiority of pitolisant vs modafinil was tested. However, the study did not attempt to directly compare the efficacy of pitolisant with modafinil.
    - A treatment difference of -3.0 points on the ESS corresponds to a decrease from severe to moderate EDS and is clinically meaningful (*Wakix FDA summary review 2019*).
    - The secondary endpoint of MWT, although not pre-specified in the statistical analysis plan, provided evidence suggesting that pitolisant had a meaningful effect on an objective measure of sleepiness (*Wakix FDA clinical review 2019*).
  - **Study limitations:**
    - The sample size was small.
    - The study took place only in Europe.
    - The study duration was short and did not provide an assessment of whether tolerance to pitolisant could develop.
    - The flexible dosing scheme and multiple patient visits may have affected the efficacy outcomes with less responsive patients being more likely to be titrated to the highest dose. Parameters for dose titration were not pre-specified, but were left to the investigator's discretion.
    - The data from this single trial did not provide definitive data about dose/dose response. No direct comparisons between the pitolisant 20 and 40 mg doses were conducted (*Wakix FDA clinical review 2019*).
    - Severely ill patients and those with unstable co-morbidities were excluded from the trial; thus, efficacy cannot be extrapolated in these populations.
    - The primary endpoint only included a subjective measure (ESS) of wakefulness.
      - Currently, the ESS scale has fallen out of favor with the FDA because it requires patients to assess a hypothetical situation with which they may or may not have had experience and is subject to recall bias. However, the FDA accepted the ESS for this application based on precedents from other narcolepsy development programs (*Wakix FDA summary review 2019*).
    - Non-inferiority of pitolisant to modafinil was not demonstrated.
    - Cataplexy rate was not assessed as a primary endpoint nor was it a pre-specified secondary endpoint.
    - Patients who were previously receiving modafinil (33% of the trial population) may have been unblinded to treatment assignment due to its effects.
    - Continuation of anticataplectic medications in a subpopulation of patients precludes extrapolation of the study findings to drug-free patients.
    - The study did not detect a difference in QoL scores or overall patient opinion on treatment in pitolisant-treated patients (*Wakix FDA clinical review 2019*).

Study 9. Wakix dossier 2019; Wakix FDA clinical review 2019. NCT 01638403 (HARMONY 1bis) (unpublished)

Study Objective: Evaluate the safety and efficacy of pitolisant in patients with EDS in narcolepsy	
Study Design, Follow-up	**Treatment Groups** (N = 166)
• 8-week, Phase 3, AC, DB, PC, PG, MC, RCT • The study was conducted in 32 sleep disorder centers in 5 European countries (Argentina, Austria, Finland, France, Germany, Hungary, Italy, Spain).	• Pitolisant (n = 67) • Modafinil (n = 66) • Placebo (n = 33) • Doses were flexibly titrated over 3 weeks to a maximum of 20 mg/day pitolisant or 400 mg/day modafinil; at the end of week 3, doses were locked and patients entered a 5-week stable-dose period. ○ For the first 7 days, all patients took a low dose (pitolisant 5 mg, modafinil 100 mg, or placebo), then a medium dose (pitolisant 10 mg, modafinil 200 mg, or placebo) for the next 7 days. On day 14, doses were adjusted based on clinical efficacy and safety.

	• A total of 76% of patients in the pitolisant group reached a dose of 20 mg. • Following the 8-week treatment period, all patients received placebo during the 1-week withdrawal phase.
Inclusion Criteria	**Exclusion Criteria**
• Age ≥ 18 years • Diagnosis of narcolepsy with or without cataplexy according to ICSD-2 (self-reported EDS occurring almost daily) with an ESS score ≥ 14 • Patients had to be free of drugs or discontinue any psychostimulant medications for ≥ 14 days at the start of the baseline period. Patients with severe cataplexy were allowed to remain on their anticataplectic medication at stable dose except TCAs; the authorized anticataplectic treatment had to be administered for ≥ 1 month prior to the trial and doses had to be stable throughout the trial.	• Any disorder that could be the main cause of EDS in patients without cataplexy (eg, sleep-related breathing disorder with apnea index ≥ 10 events/hour, apnea-hypopnea index ≥ 15 events/hour of sleep, PLM arousal index ≥ 10 events/hour, shift work, chronic sleep deprivation, or circadian sleep wake rhythm disorder) • Current or recent (within 1 year) history of a substance abuse or dependence disorder including alcohol abuse • Serious CV disorders • Severe renal or hepatic abnormalities • Psychiatric or neurological disorders • Prior severe AEs to CNS stimulants
Primary Endpoint	**Secondary Endpoints**
• Difference in mean final ESS score between the pitolisant and placebo groups after 8 weeks of treatment	• ESS responder rate (defined as final ESS score ≤ 10 or ESS score reduction ≥ 3) • MWT • SART • CGI-C • EQ-5D • PGO of treatment and symptoms of cataplexy assessed by patients' sleep diaries

- **Results:**
  - Baseline demographics (age [median 40 years], gender [50% male], ethnicity [90% Caucasian]) were similar in the 3 groups, as were symptoms of narcolepsy and baseline severity assessments (mean ESS score ~18). History of cataplexy was present in 50 (75%) patients in the pitolisant group, 50 (77%) in the modafinil group, and 26 (81%) in the placebo group. The duration of narcolepsy ranged from 10 to 15 years. The proportion of patients receiving concomitant medications was similar in the treatment groups (30.8 to 33.3%). No patients were receiving antidepressants. No patients in the pitolisant or modafinil groups were receiving sodium oxybate vs 6% in the placebo group.
  - Twelve patients prematurely withdrew from the study (pitolisant, n = 7; modafinil, n = 3; placebo, n = 2), primarily due to an AE (pitolisant, n = 4; modafinil, n = 1), patient decision (pitolisant, n = 2, modafinil, n = 1, placebo, n = 1), or lack of efficacy (pitolisant, n = 1; placebo, n = 1). There were 163 patients included in the ITT population (pitolisant, n = 66; modafinil, n = 65; placebo, n = 32). One patient in the modafinil group was withdrawn due to not fulfilling the inclusion criteria.
  - For the primary analysis, superiority of pitolisant to placebo was tested first. If pitolisant was superior to placebo (MD of ESS score statistically significant [$p < 0.05$]), then non-inferiority of pitolisant and modafinil was assessed. Non-inferiority was based on lower bound of the 95% CI of the difference (pre-defined non-inferiority value: -2).
  - The pitolisant group had a significantly greater ESS score improvement from baseline compared with placebo, demonstrating superiority. The mean change from baseline in ESS score (±SD) was -4.5 (4.6) for pitolisant and -3.7 (5.6) for placebo (treatment effect: -2.12; 95% CI, -4.10 to -0.14; $p = 0.036$).
  - The mean change from baseline in ESS score (±SD) was -7.8 (5.8) for modafinil.
    - The non-inferiority of pitolisant compared to modafinil could not be concluded (treatment effect: 2.83; 95% CI, 1.10 to 4.55; $p = 0.002$), most likely due to an imbalance between dosages of both drugs and the short treatment period; the upper dose of pitolisant was limited to 17.8 mg daily (one-half the maximum dose allowed in other trials), while modafinil was titrated up to the recommended dosing of 200 mg or 400 mg daily. Between 66% and 79% of patients were taking modafinil 400 mg daily.
  - The ESS responder rate (final ESS score ≤ 10 or ESS score reduction ≥ 3) was significantly greater in the pitolisant group (64.2%) compared to the placebo group (34.4%) (RR 2.10; $p = 0.002$). Pitolisant treatment resulted in fewer ESS responders compared to modafinil (43 [64.2%] vs 50 [76.9%], respectively), but this difference was not statistically significant (RR: 0.86; $p = 0.052$). Superiority of pitolisant was seen over placebo in MWT values. The values decreased from baseline in the placebo group but improved in the pitolisant group ($p = 0.022$). MWT also improved from baseline in the modafinil group; however, no statistically significant difference between pitolisant and

modafinil was seen (p = 0.198). The NO GO error scores in the SART decreased in the pitolisant group, with a statistically significant treatment difference compared with placebo (p = 0.002); changes in the modafinil and pitolisant groups were not statistically different. No significant difference on the EQ-5D scores or PGO was found between pitolisant and the placebo group. Results of the secondary endpoints are shown in Table 6.

Table 6. Secondary endpoint results (ITT population)

Endpoint	Pitolisant (n = 67)	Modafinil (n = 65)	Placebo (n = 32)
ESS responder (final ESS score ≤ 10 or ESS score reduction ≥ 3), n (%)			
Change	43 (64.2%)	50 (76.9%)	11 (34.4%)
Relative risk	Pitolisant vs placebo: 2.10; p = 0.002 Pitolisant vs modafinil: 0.86; p = 0.052		
MWT			
Baseline	6.65	5.84	7.90
Final	7.79	7.45	6.51
Change (ratio of final/baseline)	1.17	1.28	0.82
Treatment effect, ratio of mean change (95% CI)	Pitolisant vs placebo: 1.57 (1.12 to 2.20); p = 0.022 Pitolisant vs modafinil: 1.05 (0.80 to 1.38); p = 0.198		
SART-NO GO			
Baseline	8.21	8.88	7.53
Final	6.73	6.50	7.76
Change (ratio of final/baseline)	0.82	0.73	1.03
Treatment effect, ratio of mean change (95% CI)	Pitolisant vs placebo: 0.77 (0.65 to 0.91); p = 0.002 Pitolisant vs modafinil: 0.92 (0.79 to 1.07); p = 0.259		
SART-GO			
Baseline	3.23	2.94	3.05
Final	2.71	2.33	2.60
Change (ratio of final/baseline)	0.84	0.79	0.85
Treatment effect, ratio of mean change (95% CI)	Pitolisant vs placebo: 0.99 (0.77 to 1.27); p = 0.910 Pitolisant vs modafinil: 0.94 (0.73 to 1.21); p = 0.641		
SART-total			
Baseline	11.08	11.71	10.54
Final	8.90	8.44	9.94
Change (ratio of final/baseline)	0.82	0.74	0.94
Treatment effect, ratio of mean change (95% CI)	Pitolisant vs placebo: 0.83 (0.6 to 0.99); p = 0.043 Pitolisant vs modafinil: 0.93 (0.77 to 1.11); p = 0.407		
Cataplexy rate (arithmetic mean)			
Baseline	0.84	0.87	1.25
Final	1.69	0.79	1.85
Change, MD (± SD)	0.85 (3.75)	−0.33 (1.02)	0.59 (1.16)
Treatment effect, MD (95% CI)	Pitolisant vs placebo: −1.00 (−2.12 to 0.13); p = 0.077 Pitolisant vs modafinil: 0.05 (−0.55 to 0.65); p = 0.865		
CGI-C EDS improved, n (%)	44 (65.7%)	49 (75.4%)	11 (34.4%)
CGI-C cataplexy improved, n (%)	31 (46.3%)	32 (49.2%)	10 (31.3%)
PGO improved, n (%)	14 (20.9%)	28 (43.1%)	9 (28.1%)

- TEAEs were reported in 34 (50.7%) patients in the pitolisant group, 31 (47.7%) patients in the modafinil group, and 13 (39.4%) patients in the placebo group. The most frequent AEs were headache in all 3 groups; nausea, nasopharyngitis, and dizziness in the pitolisant group; nasopharyngitis in the modafinil group; and dizziness, diarrhea, insomnia, and fatigue in the placebo group. There were no serious AEs reported during the study. There were 19 severe AEs, 8 of which were regarded as treatment-related: 5 with pitolisant (cataplexy, n = 2; somnolence, n = 2; abdominal pain, n = 1) and 3 with modafinil (somnolence, migraine, abdominal pain, each n = 1).
- Patients in the placebo group experienced significant decreases from baseline in systolic and diastolic BP compared to those in the pitolisant or modafinil groups. No patients in the pitolisant group were reported to have withdrawal syndrome, whereas 1 patient in the modafinil group and 1 in the placebo group met the criteria for withdrawal syndrome.
- The mean change from baseline in Beck Depression Inventory (BDI) was similar between groups: pitolisant, -1.7; modafinil, -1.3 and placebo, -1.1 (p = 0.547).
  - The BDI Short Form scores indicated presence of depression (≥ 6) or indicated suicide risk (score of > 0 on BDI item G). The BDI-SF is a 13-question self-report measure of depression severity. Scores on each question can

range from 0 to 3 on a Likert scale; the maximum total score on the questionnaire is 39. Scores of 0 to 4 indicate minimal depression, 5 to 7 indicate mild depression, 8 to 15 indicate moderate depression, and 16 to 39 indicate severe depression. The BDI-SF asks about sadness, guilt, energy level, appetite, and depressive cognitions, and Item G asks specifically about suicidal ideation (*Wakix FDA clinical review 2019*).

- **Conclusion:**
  - Pitolisant, dosed up to 20 mg once daily, was efficacious on EDS compared with placebo. The effects of pitolisant (up to a submaximal dose of 20 mg/day) and modafinil (up to 400 mg/day) on all EDS measures did not differ substantially. In addition, all 3 treatments were considered to be well tolerated. Withdrawal syndrome was seen with modafinil but not with pitolisant.
- **Study Appraisal:**
  - **Study sponsorship:**
    - Bioprojet, France
  - **Study rating:**
    - N/A
  - **Study strengths:**
    - Although not as impressive as the results of the HARMONY I study, a decrease of 2 points on the ESS is still considered clinically meaningful based on published literature. The maximum dose of pitolisant in this study was 20 mg (whereas it was 40 mg in HARMONY I) (*Wakix FDA summary review 2019*).
    - The lack of effect on cataplexy could have been related to the lower maximum dose (20 mg) as compared with the dose in HARMONY 1 and HARMONY CTP (40 mg) (*Wakix FDA clinical review 2019*).
    - The secondary endpoint of MWT, although not pre-specified in the statistical analysis plan, provided evidence suggesting that pitolisant had a meaningful effect on an objective measure of sleepiness (*Wakix FDA clinical review 2019*).
  - **Study limitations:**
    - The sample size was relatively small.
    - The study took place only in Europe.
    - The study duration was short.
    - The trial did not assess persistence of effect after treatment was discontinued (*Wakix FDA clinical review 2019*).
    - The primary endpoint only included a subjective measure (ESS) of wakefulness.
    - Non-inferiority of pitolisant to modafinil was not demonstrated, likely due to the imbalance in pitolisant and modafinil dosing selection.
    - The data from this single trial did not provide definitive data about dose/dose response. No direct comparisons between the pitolisant 20 and 40 mg doses were conducted (*Wakix FDA clinical review 2019*).
    - Cataplexy was not assessed as a primary or a pre-specified secondary endpoint.
    - The study did not detect a difference in QoL scores or overall patient opinion on treatment in pitolisant-treated patients (*Wakix FDA clinical review 2019*).
    - Severely ill patients and those with unstable co-morbidities were excluded from the trial; thus, efficacy cannot be extrapolated in these populations.

Study 10. Dauvilliers et al, *Sleep*. 2019;21;42(11):1-11 (HARMONY 3)

Study Objective: Evaluate the safety and maintenance of efficacy of pitolisant in the long-term in the treatment of EDS in patients with narcolepsy with or without cataplexy	
Study Design, Follow-up	**Treatment Group** (N = 102, 75 with cataplexy)
• 12-month, Phase 3, OL, single-arm, MC, longitudinal, uncontrolled trial • Patients were recruited from 7 centers in France and 1 in Hungary	• Pitolisant • Eligible patients went through a 1-month individual titration period at the initiation of treatment, except for patients coming from the French Compassionate Use Program (CUP) who were already treated by pitolisant and could continue at their established dose at inclusion. • Patients received pitolisant 5 mg once daily for the first 7 days, and 10 mg for the next 7 days. Then, during the third week, the dose could be increased up to 20 mg once daily if safety and tolerability were good and, during the fourth week, doses could be adjusted according to individual benefit/tolerance ratio between 5 to 20 mg once daily. After 1 month, the dose could be increased

	to 40 mg once daily if the investigator judged that the efficacy of 20 mg was not sufficient. Thereafter, the dose remained stable for a 2-month period. During the follow-up visits scheduled in all patients at 3, 6, 9, and 12 months, an individual dose adjustment could be performed again (5, 10, 20, or 40 mg once daily). • Six patients dropped out before being titrated to 40 mg (4 at 1 month and 2 at 3 months).
Inclusion Criteria	**Exclusion Criteria**
• Age ≥ 18 years • Diagnosis of narcolepsy with or without cataplexy and ESS score ≥ 12 ○ When typical cataplexy was not present, an overnight PSG followed by a positive MSLT within the past 5 years had to show a mean sleep latency ≤ 8 minutes with ≥ 2 sleep-onset rapid eye movement periods. • Patients could be naive to pitolisant ("*de novo*" subgroup) or formerly treated with pitolisant ("exposed" subgroup) during previous single-blind or DB studies or have been switched from the CUP to this study.	• Any other cause of daytime sleepiness, including an untreated sleep apnea syndrome sleepiness • History of substance abuse, severe psychiatric, or neurological disorder • Serious CV disorder • Severe hepatic or renal impairment • Use of TCAs or H_1-receptor antagonists
Primary Endpoint	**Secondary Endpoints**
• Incidence of TEAEs at 12 months	• BDI • ESS score and responder rate • CGI-C • EQ-5D • Symptoms in patient sleep diaries (partial and generalized cataplexy attacks, hypnagogic hallucinations, sleep paralysis, and sleep attacks)

• **Results:**

○ The study group included 73 *de novo* patients (52 with cataplexy) and 13 exposed patients (11 with cataplexy) with a period of at least 3 months without pitolisant between a previous participation in a pitolisant trial (except 1 with only a 1-week washout); all 86 patients had an up-titration at the start of the study. The other 16 exposed patients (12 with cataplexy) were directly switched from the French CUP and were included at their previous established dose without titration. Hence the length of exposure to pitolisant was longer for the subgroup of previously exposed patients (mean 548 days ± 308 days) as some of them were treated since more than 1 year in the CUP before being enrolled in this study, whereas "*de novo*" patients were exposed for a maximum of 1 year (mean 260 ± 143 days). Two thirds (N = 68) of treated patients completed the 12-month treatment period: 60.3% of the *de novo* patients (N = 44, 31 with cataplexy) and 82.8% of the previously exposed patients (N = 24, 20 with cataplexy).

○ At inclusion, the subgroup of exposed patients (N = 29), including those already treated in the CUP, had a lower mean ESS score than *de novo* patients. They also had a better health status evaluated with EQ-5D and less depressive symptoms as assessed by a lower BDI score. Eighteen patients of the whole population (17.6%) had history of depression or depressive syndrome, with 9 (8.8%) suffering from an ongoing depression at baseline.

○ During the 12 months of treatment, 52.9% of patients were receiving co-medications, the most frequent being methylphenidate (22.5%) and modafinil (17.6%). The co-medications taken at inclusion remained unchanged during the study in 37% of patients, increased (or new treatment added) in 50%, decreased in 7.4% or were discontinued in 5.5%.

○ At 3 months of treatment, 67.5% (56/83) of patients were taking 40 mg pitolisant QD. At the end of the 12 months, 76.5% (52/68) of the completers were treated with the 40 mg daily dose and among them, 65.4% were on monotherapy.

○ Overall, 34 (33.3%) patients prematurely discontinued the trial, mainly during the first 3 months (31/34), including 29 *de novo* patients (39.7% of this subgroup) and 5 (17.2%) exposed patients.

Safety

○ During the first 12-month treatment period, a total of 58 patients (56.9%) reported 168 TEAEs. The TEAE frequency tended to decrease with time: 54.8% (92/168) were observed during the first 3 months and 12.5% (21/168) during the last 3 months. Overall, 43.5% of TEAEs were considered related to the study drug: migraine (n = 2), insomnia (1), irregular sleep (1), nausea (1), depression (1), rash (1), vertigo (1), libido decrease (1), premature ejaculation

(1), spontaneous abortion (1). The most common TEAEs were headache (11.8%), insomnia (8.8%), weight gain (7.8%), anxiety (6.9%), depression (4.9%), and nausea (4.9%). Most TEAEs were mild to moderate; only 22 (13.1%) were severe, of which only half were considered related to the study drug. Seven patients (6.9%) experienced a serious (all non-life-threatening) TEAE. All serious TEAEs were unrelated to pitolisant, except 1 miscarriage that was possibly related. The proportion of treatment-related TEAEs was twice as great in the subgroup who took additional anti-narcoleptic agents in comparison to patients treated with pitolisant alone (53.7 vs 29.2%; p = 0.012).

- TEAE frequency was not substantially increased or different in subpopulations including the elderly (≥ 65 years of age), patients with depressive symptoms at inclusion, patients with CV or gastrointestinal disorders, renal impairment, hepatic impairment, patients with allergies, patients receiving a concomitant treatment with a possible CYP450 interaction (eg, paroxetine), or patients treated with SSRIs only.
- Five cases of depression were reported during the 12-month treatment period. Two of them were considered related to the study drug. The proportion of patients with moderate or severe depressive symptoms (BDI score ≥ 8) was relatively stable during the trial (16.6% at baseline vs 19.1% at 12 months).

Efficacy

- Sleepiness
  - Compared to baseline, the mean ESS score (± standard error [SE]) decreased from the first month of treatment (-3.37 ± 0.42; n = 93) and continued to decline after 3 (-4.39 ± 0.51) and 6 months (-4.90 ± 0.54). This change occurred at a similar rate in the *de novo* or previously exposed patients. In the whole patient population who completed the 12-month treatment (n = 68), the mean decrease from baseline in ESS score was -4.6 ± 0.59 at the end of the period. With last observation carried forward (LOCF) method applied to the missing data of the whole population (N = 102; ie, taking into account the patients who left the trial before 12 months), the reduction was -4.0 ± 0.49. The decrease was significant whether patients had previously been exposed to pitolisant or not (p < 0.001 for both) and of similar magnitude in both subgroups (-4.2 and -4.9, respectively).
  - At the end of the 12-month treatment period, two-thirds of patients were ESS responders with minimum decrease of 3 units; the highest responder rate was observed in the *de novo* subgroup (70.5%). More than one-third of patients (25/68) had normalized sleepiness (ESS < 11) at 12 months (27.3% for *de novo* patients and 54.2% for exposed patients); their mean ESS score decreased from 15.3 ± 0.6 at baseline to 6.6 ± 0.6 at 12 months. In the 44 patients (among 68) who completed a diary at 12 months, the mean daily number of sleep attacks decreased by 27% (from 1.36 ± 0.21 to 0.99 ± 0.14; change -0.37; 95% CI, -0.80 to 0.06).
- Cataplexy
  - In the subgroup of patients with completed sleep diaries (n = 44), the number of complete (generalized) cataplexy attacks per day decreased by 76% between baseline (0.33 ± 0.25) and 12 months (0.08 ± 0.05): change -0.25; 95% CI, -0.67; 0.17]), and by 65% (from 0.77 ± 0.37 to 0.27 ± 0.08 per day; change -0.49; 95% CI, -1.09 to 0.10) for partial cataplexy. The mean daily number of all (generalized and partial) cataplexy episodes decreased by 68% between baseline and 12 months (1.09 ± 0.53 to 0.35 ± 0.10 per day; p = 0.055). Considering the subgroup of *de novo* patients on pitolisant monotherapy (N = 15), generalized and partial cataplexy attacks were reduced by 80% (0.71 to 0.14 per day) and 82% (0.93 to 0.17 per day), respectively.
- Other symptoms
  - The mean frequency of hallucinations decreased by 54% between baseline and 12 months (from 0.13 ± 0.06 to 0.06 ± 0.03 per day; change -0.06 [95% CI, -0.14 to 0.01]). The mean frequency of sleep paralysis was reduced by 63% (from 0.16 ± 0.06 to 0.06 ± 0.04, change -0.10 [95% CI, -0.21 to 0.00]; p = 0.023). The EQ-5D score improved in *de novo* (from 62.1 ± 2.4 at baseline to 71.2 ± 2.6 at 12 months; p < 0.001) patients and, to a lesser extent, in previously exposed patients (from 71.8 ± 3.0 at baseline to 74.5 ± 2.9 at 12 months). The CGI-C improved for almost all patients who completed the 12-month treatment period (93.2% and 95.6% of *de novo* and exposed patients, respectively). The total duration of nocturnal sleep remained unchanged.

Five-year extension phase (*Wakix dossier 2019*)

- The 5-year extension phase included a total of 77 French patients who received pitolisant; 16 ATU patients had already been treated through the CUP before entering the 5-year extension phase of the study and 61 patients were considered naïve to treatment. The baseline demographics and characteristics were similar between groups.
- The mean length of pitolisant exposure for naïve patients (n = 31) and ATU patients (n = 16) was 799 days and 1859 days, respectively.
- The most commonly reported TEAEs were headache (19.5%), weight gain (18.2%), insomnia (11.7%), anxiety (11.7%), depression (11.7%), and nausea (11.7%).The incidence of TEAEs decreased over time, with the highest incidence during Month 1 (16.6%) and < 10% after Month 6.
- Throughout the entire study extension treatment period, 26 (33.8%) patients reported TEAEs leading to temporary or permanent discontinuation of study treatment. The number of patients with TEAEs was higher in subgroups with pitolisant prescribed as add-on therapy to pre-existing narcolepsy treatments, particularly when added to psychostimulants, and the number of patients with TEAEs was lowest in the pitolisant monotherapy subgroup.

- At enrollment, 15 (19.5%) patients had a history of depression or depressive syndrome. Six new cases of depression occurred during the study, but only 3 were considered to be treatment-related. The overall BDI evaluation did not show any increase in depressive symptom severity.
- EDS, measured by ESS score, decreased during the first 12 months of the study, and the reduction was maintained throughout the 5-year extension. The mean ESS score (±SD) of the overall 5-year extension study population decreased from baseline by -3.47 (4.20) at month 1 and continued to decrease at months 3 and 6, with a mean score reduction (±SD) from baseline of -4.03 (4.70) and -4.22 (4.54), respectively. The reduction in ESS score (±SD) was maintained up to the end of the 12-month period and continued during the extended follow-up period, with −4.41 (5.38) after 2 years of treatment (n = 45), -4.45 (6.16) after 3 years of treatment (n = 38), -4.76 (5.73) after 4 years of treatment (n = 34), and -6.07 (7.19) after 5 years of treatment (n = 14).
- Sleep diaries were collected from all compliant patients who had completed their diaries as requested; this included 34 patients at baseline; 32 patients at month 3; 25 patients at months 12 and 18; 17 patients at year 2; 14 patients at year 3; and 2 patients at year 5. The mean daily number of total and partial cataplexy episodes, as well as hallucinations, improved during the 5-year extension phase; at the end of the first 12-month treatment period, total cataplexy episodes, partial cataplexy episodes, and hallucinations decreased by 87.2%, 60%, and 50%, respectively, and this reduction was maintained throughout the extended follow-up period for patients who continued. Other sleep parameters remained relatively stable or improved slightly.

- **Authors' Conclusion:**
  - Pitolisant was well tolerated and improved most major narcolepsy symptoms when given alone or in combination with other anti-narcoleptic agents for a long period. It remains to be definitively determined whether it constitutes a useful first-line therapy for patients with narcolepsy.
- **Study Appraisal:**
  - **Study sponsorship:**
    - Bioprojet, France
  - **Study limitations:**
    - There was potential for selection bias, both in the patients who entered the study from the CUP who had been on pitolisant previously, as well as from those who dropped out (nearly one-third), during the 1-year treatment period. Patients already exposed to pitolisant were more likely to be compliant, being *a priori* good responders with good tolerance.
    - Since the study did not include a placebo or a control group, it did not provide conclusive data about the duration of pitolisant's treatment effect (*Wakix FDA clinical review 2019*).

Study 11. Szakacs et al, *Lancet Neurol.* 2017;16:200-207 (HARMONY CTP)

Study Objective: Evaluate the safety and efficacy of pitolisant in patients with narcolepsy with cataplexy	
Study Design, Follow-up	**Treatment Groups** (N = 105)
• 7-week, Phase 3, DB, MC, PC, RCT • The study was conducted in 16 sleep disorder centers in 9 countries (Bulgaria, Czech Republic, Hungary, Macedonia, Poland, Russia, Serbia, Turkey, and Ukraine)	• Pitolisant (n = 54) • Placebo (n = 51) • Treatment included 3 weeks of flexible dosing (5 mg, 10 mg, or 20 mg once daily) followed by 4 weeks of stable dosing (5, 10, 20, or 40 mg once daily). ○ During the flexible dosing period, patients took 5 mg of pitolisant or placebo once a day for the first 7 days, then 10 mg of pitolisant or placebo once a day for the next 7 days. ○ During the week 2 visit, the dose was assessed and could remain at 10 mg, be increased to 20 mg, or decreased to 5 mg by the investigators on the basis of individual clinical efficacy and safety; no specific recommendations were provided to investigators for dose adjustment. ○ At visit 3, investigators adjusted doses again to establish the final dose (5, 10, 20, or 40 mg) for the 4-week stable dosing period. ○ At the end of the stable dosing period, all patients entered a 1-week withdrawal period during which time they received placebo.

	• In the stable dosing phase, 64.8% of patients (35/54) in the pitolisant group received the maximum dose of 40 mg.
Inclusion Criteria	**Exclusion Criteria**
• Age ≥ 18 years • Diagnosis of narcolepsy with cataplexy according to the ICSD-2 criteria • Three or more cataplexies per week and an ESS score ≥ 12 • Ongoing anticataplectic treatment with sodium oxybate or antidepressants was allowed if doses were stable for ≥ 1 month before randomization and throughout the trial.	• Any other disorder with EDS (eg, sleep-related breathing disorder with sleep apnea index ≥ 10 per hr or apnea or hypopnea index of ≥ 15 per hr, or a PLM disorder with arousal index of ≥ 10) • History of substance abuse • Serious CV disorder • History of substance abuse • Serious CV disorder • Severe hepatic or renal abnormalities • Psychiatric disorder • Concomitant use of psychostimulants or sedative medications
Primary Endpoint	**Secondary Endpoints**
• Change in the average number of cataplexy attacks per week between the 2 weeks of baseline and the 4 weeks of stable dosing (WCR).	• WCR changes in patients maintained or not in their anticataplectic treatment • Mean change in ESS score • Proportion of patients with final ESS score ≤ 10 (a validated cutoff) • Proportion of patients with abnormally high cataplexy rate (WCR > 15, a non-validated cutoff corresponding to the median of the sample) • MWT • CGI-C • PGO on efficacy • EQ-5D • Number of days with hallucinations

- **Results:**
  - Baseline demographics and narcolepsy characteristics of the 2 groups were similar. The number of cataplexy episodes per week was 11 in the pitolisant group and 9.2 in the placebo group at pre-screening. The mean ESS score was 17.3 in the pitolisant group and 17.1 in the placebo group. In the previous 3 months, 41% of patients in the pitolisant group had received ≥ 1 anticataplectic medication vs 80% in the placebo group. The percentages of patients continuing anticataplectic medications during the trial were 7% in the pitolisant group and 16% in the placebo group.
  - Five patients from the pitolisant group and 9 patients from the placebo group (13.3%) withdrew from the study; 8 patients did not comply (7 in the placebo group and 1 in the pitolisant group), 4 showed lack of efficacy (2 in each group) and 2 patients from the pitolisant group were unable to continue study visits.
  - The reduction of cataplexy by 75% in the pitolisant group ($WCR_{f/b}$ = 0.25) was significantly higher than in the placebo group (38%; $WCR_{f/b}$ = 0.62; rR = 0.51, 95% CI, 0.44 to 0.60, p < 0.0001, Table 7).
    - In post-hoc analyses, this effect remained significant (all p < 0.0001) for each subgroup of patients receiving 10 mg (n = 7), 20 mg (n = 9), or 40 mg (n = 35) as their stable dose.
    - By comparing WCR in both groups at each week, a significant benefit of pitolisant was observed from week 5, improving until the last week (rR = 0.37, 95% CI, 0.07 to 0.69). In a pre-specified analysis, the effect of pitolisant was unchanged, irrespective of whether patients used concomitant anticataplectic treatment pre-inclusion. The geometric mean of the ratio $WCR_{f/b}$ for patients who were receiving concomitant anticataplectic treatment (rR 0.49, 95% CI, 0.31 to 0.82, n = 12) or did not receive this medication (rR 0.51, 0.11 to 2.28, n = 93) were not significantly different ($p_{interaction}$ = 0.455).
  - Superiority of pitolisant was observed for most of the secondary endpoints (Table 7).

Table 7. Primary and secondary endpoint efficacy results (ITT population)

Endpoint	Pitolisant (n = 54)			Placebo (n = 51)			Treatment effect	
	Baseline	Final	Change	Baseline	Final	Change	Effect (95% CI)	p-value
WCR*	9.15	2.27	0.25	7.31	4.52	0.62	0.51 (0.43 to 0.60)	< 0.0001
WCR > 15 (n/N[%])	15/54 (28%)	4/54 (7%)	--	9/51 (18%)	12/51 (24%)	--	0.05 (0.01 to 0.40)	0.005

ESS score	17.4	12.0	-5.4	17.3	15.4	-1.9	-3.48 (-5.03 to -1.92)	0.0001
ESS responders	--	20/51 (39%)	--	--	9/50 (18%)	--	3.28 (1.08 to 9.92)	0.035
MWT (min)‡	3.54	6.91	1.95	4.08	4.32	1.06	1.85 (1.24 to 2.74)	0.003
Improvement in GCI cataplexy (n/N[%])	--	36/54 (67%)	--	--	17/51 (33%)	--	4.00 (1.54 to 10.38)	0.004
Improvement in CGI EDS	--	37/54 (69%)	--	--	12/51 (24%)	--	7.07 (2.55 to 19.59)	0.0002
Improvement in PGO (score < 3, n/N[%])	--	43/54 (79%)	--	--	22/51 (43%)	--	--	--
EQ-5D sum score†	6.4	6.0	-0.4	6.5	6.4	-0.1	-0.33 (-0.70 to 0.03)	0.075
No. of hallucinations per week*	0.41	0.16	0.39	0.57	0.32	0.57	0.50 (0.31 to 0.83)	0.007

*WRC was the primary outcome; the geometric mean was calculated and 0 values replaced with 0.1; change calculated as the final value/baseline measurement; treatment effect analyzed as a ratio rate derived from Poisson regression after adjusting to baseline.
†Arithmetic mean; change calculated as final measurement-baseline measurement; treatment effect derived from a linear model adjusting for baseline.
‡Geometric means; change calculated as the final value/baseline measurement; treatment effect derived from linear model of log-transformed values and adjusted for baseline. Other statistical analyses used logistical regression to identify odds ratio.

- In the pitolisant group, 19 (35%) patients reported AEs vs 16 (31%) in the placebo group (p = 0.528).
- The most frequent AEs were headache for both treatment groups; irritability, anxiety, and nausea for the pitolisant group; and somnolence for the placebo group.
- Double the number of AEs were considered treatment-related with pitolisant compared with placebo (28% [15 of 54 in the pitolisant group vs 12% [6 of 51] in the placebo group; p = 0.048), but all were of mild-to-moderate intensity, except for 1 case of severe nausea that resolved without sequelae after pitolisant discontinuation.
- BDI score decreased significantly between baseline and end of treatment in the pitolisant group compared with placebo (-1.8 vs -0.8; p = 0.02). Duration of nocturnal awakenings also did not differ significantly between groups. No withdrawal syndrome was reported with pitolisant, although 1 was observed with placebo.

- **Authors' conclusion:**
  - Pitolisant was well tolerated and could be useful to improve not only cataplexy but also EDS and hallucinations in patients with narcolepsy. If confirmed in long-term studies, pitolisant might constitute a useful first-line therapy for cataplexy in patients with narcolepsy, for whom there are currently few therapeutic options.
- **Study Appraisal:**
  - **Study sponsorship:**
    - Bioprojet, France
  - **Study rating:**
    - Fair
  - **Study strengths:**
    - The study enrolled patients with severe cataplexy.
    - A pre-specified analysis examined the effect of concomitant anticataplectic medication in reducing the WCR.
  - **Study limitations:**
    - The sample size was small.
    - The study duration was short and did not provide an assessment of whether tolerance to pitolisant could develop.
    - The flexible dosing scheme and multiple patient visits may have affected the efficacy outcomes with less responsive patients being more likely to be titrated to the highest dose.
      - A pooled analysis of dose-response conducted by the applicant in the ITT populations in HARMONY 1, HARMONY 1bis, and HARMONY CTP found that pitolisant appeared to have a linear dose-response effect (*Wakix FDA clinical review 2019*).

Study 12. Lehert & Falissard, *Sleep.* 2018;41(12):1-13

Study Objective: Evaluate the safety and efficacy of medical treatments for narcolepsy using a network meta-analysis	
Study Design, Follow-up	**Treatment Groups**
• Network meta-analysis (N = 14 RCTs) • All of the studies were of short duration, from 2 to 12 weeks	• Modafinil (n = 10 RCTs) • Pitolisant (n = 3 RCTs) • Sodium oxybate (n = 4 RCTs) • Ten, 4, and 3 studies compared modafinil, sodium oxybate, and pitolisant with placebo, respectively. Eight

	studies compared only 1 treatment with placebo, whereas the 6 other studies compared multiple treatments, respectively (3 or 4 treatments). For the 4 studies of sodium oxybate, the 2 studied dosages 6 and 9 g/d were compared in 3 studies, whereas the low dose (6 g/d) was only compared with placebo in 1 study. Three studies assessed pitolisant: 2 for the 40 mg and 1 study for the 20 mg dose (unpublished, results available).
Inclusion Criteria	**Exclusion Criteria**
• RCTs enrolling adults with narcolepsy with or without cataplexy • RCTs comparing the identified treatment with placebo, as well as comparisons with other treatments • RCTs that provided data on at least 1 of the following selected outcomes for both efficacy and safety: the ESS, the MWT, number of cataplexy attacks during the treatment exposure, and safety reporting of AEs during the treatment exposure	• Non-randomized trials • Retrospective studies • Trials not assessing ≥ 1 efficacy or safety endpoint
Primary Endpoints	**Secondary Endpoints**
• EDS measured by ESS and MWT • WCR ○ To provide a unique primary endpoint and to reduce type 1 multiplicity in the analysis, the ESS and MWT were combined into the EDS mean Z score, to define the narcolepsy score (NS) as the mean of EDS and WCR Z scores (ESS and WCR used minus their values such that larger values indicated patient improvement).	• Overall safety score (OSS), defined as the TEAE incidence rate during the exposure period • Benefit/risk (B/R) ratio ○ The unitless BR ratio was defined as the residual value of the linear fit between NS and OSS, or the simple ratio NS/OSS.

- **Results:**
  - Network meta-analysis compared the efficacy and safety of multiple treatments, multi-arm studies, and multi-criteria treatment decisions, based on a random-effects model that assumed heterogeneity between studies, with corrections for multi-arm studies.
  - Armodafinil studies were pooled with modafinil studies; however, a comparison between the 2 groups was conducted to confirm the relevance of this method.
  - Treatment ranking by P scores measured the extent of certainty that any one treatment was better than another treatment, averaged over all competing treatments, equivalently with the surface under the cumulative ranking curve (SUCRA) defined as the rank of treatment within the range of treatments.
  - Most of the included trials were acceptable for internal validity, external validity, and statistical methodology.
    - In 1 study, the 2 study arms were selected after 16 weeks of OL modafinil, potentially favoring the modafinil group over the placebo group.
    - In *Black & Houghton 2006* (see study 14), all patients were treated with modafinil at the established dose until randomization, and the abrupt withdrawal from modafinil potentially created an artificially worsened placebo group when treatment arms were changed. In this study, the highest doses of sodium oxybate were given without previous titration, unlike as in other trials, and this may have penalized the drug safety profile.
  - For ESS (12 studies), only 3 interventions reached a significant MD when compared with placebo: pitolisant 40 mg (-3.05; 95% CI, -5.24% to -0.85%; p < 0.001), sodium oxybate 9 g (-2.94; 95% CI, -5.04% to -0.85%; p < 0.001), and modafinil (-2.37; 95% CI, -3.41% to -1.32%; p < 0.001), without statistical differences between them. Homogeneity across studies (p = 0.16), and slight between-design inconsistency (p = 0.02) were found.
  - The MWT (12 studies) measured the mean changes in time (minutes) from baseline. There was significant heterogeneity across studies (p < 0.001), and no between-day design inconsistency (p = 0.601) was found. Significant relative benefits when compared with placebo were found for pitolisant 40 mg (4.88 min; 95% CI, 0.57% to 9.20%; p = 0.009) and modafinil (1.85 min; 95% CI, 0.16% to 3.55%; p < 0.001).
  - Cataplexy was reported in 8 studies, and the difference between treatments was calculated by standardized mean difference (SMD) converted by linear calibration into decrease of weekly rate of cataplexies (DWCR). Significant reductions were observed for pitolisant 40 mg (SMD = -0.52; 95% CI, -0.90% to -0.13%; p < 0.001) (DWCR = -5.9) and sodium oxybate 9 g (SMD = -0.41; 95% CI, -0.79% to 0.032%; p = 0.023) (DWCR = -5.2). No marked or significant heterogeneity across studies (p = 0.51) or between-design inconsistency (p = 0.09) were found.

- **Authors' conclusion:**
  - Modafinil (200 to 400 mg/d), sodium oxybate 9 g/d, and pitolisant up to 40 mg/d had similar efficacy in reducing EDS. Only sodium oxybate 9 g/d and pitolisant up to 40 mg/d demonstrated a comparable beneficial effect on cataplexy. Overall, pitolisant at a maximal dose of 40 mg/d was shown to have a slightly better safety profile and the highest BR ratio.
- **Study Appraisal:**
  - **Study sponsorship:**
    - Bioprojet Pharma
    - The authors are consultants for Bioprojet Pharma.
  - **Study rating:**
    - N/A
  - **Study strengths:**
    - The network meta-analysis compared 6 different interventions involving placebo, modafinil, pitolisant, and sodium oxybate.
  - **Study limitations:**
    - Sodium oxybate and pitolisant were both compared with placebo and modafinil, but not between each other. Methodological issues exist for comparing sodium oxybate in the context of RCTs; unlike the other drug treatments, sodium oxybate induces deep sleep and has multiple contraindications, which would make blinding difficult or impossible.

Sodium oxybate/oxybate salts

Narcolepsy with cataplexy

Study 13. Alshaikh et al, *J Clin Sleep Med.* 2012;8(4):451-458

Study Objective: Evaluate the efficacy and safety of sodium oxybate in narcolepsy-cataplexy patients	
Study Design, Follow-up	**Treatment Groups** (N = 741)
• Systematic review and meta-analysis (N = 6 RCTs and 5 companion reports) • The duration of the RCTs ranged from 4 to 8 weeks, except for 1 study that lasted for 12 weeks. Sodium oxybate at a dose range between 4.5 to 9 g/night was the dose evaluated in most of the studies.	• Sodium oxybate • Placebo • Modafinil • One study assessed the combination of sodium oxybate and modafinil vs sodium oxybate and modafinil alone.
Inclusion Criteria	**Exclusion Criteria**
• RCTs evaluating sodium oxybate in patients with narcolepsy and cataplexy (published or unpublished)	• Non-RCTs
Primary Endpoint	**Secondary Endpoints**
• Elimination of EDS according to subjective or objective indicators.	• QoL using the SF-36 scale • CGI-C

- **Results:**
  - All of the included studies excluded patients with other sleep disorders. The percentage of females ranged from 50 to 65%. One study that assessed the effect of sodium oxybate on EDS did not include cataplexy as an enrollment criterion.
  - None of the included RCTs were assessed as having adequate sequence generation or allocation concealment. All of the studies adequately blinded participants and addressed incomplete outcome data. Five of the 6 studies were free from selective outcome reporting. All of the studies scored unclear on other biases, as they involved private-industry funding. Four of the included studies were sponsored by the manufacturer.
  - Sodium oxybate (usually 9 g/night) was superior to placebo for reducing mean weekly cataplexy attacks (n = 2 RCTs, MD -8.46, 95% CI, -15.27 to -1.64), heterogeneity: I^2 = 0%, test for overall effect: Z = 2.43 [p = 0.01]); increasing the MWT (n = 2 RCTs, MD 5.18, 95% CI, 2.59 to 7.78, I^2 = 0%, Z = 3.93 [p < 0.0001]); and reducing sleep attacks (n = 2 RCTs, MD -9.65, 95% CI, -17.72 to -1.59), I^2 = 13%, Z = 2.35 [p = 0.02]).
  - Data from 3 RCTs indicated an increase in CGI-C scores (RR 2.42, 95% CI, 1.77 to 3.32, I^2 = 0%, Z = 5.53 [p < 0.00001).
  - Sodium oxybate did not significantly increase REM sleep vs placebo (n = 2 RCTs, MD -0.49, 95% CI, -3.90 to 2.92, I^2 = 0%, Z = 0.28 [p = 0.78]).

- Patients receiving sodium oxybate (9 g per night) experienced more AEs vs placebo, including nausea (n = 3 RCTs, RR 7.74, 95% CI, 3.15 to 19.05, I^2 = 0%, Z = 4.45 [p < 0.00001]), vomiting (n = 2 RCTs, RR 2.87, 95% CI, 0.84 to 9.80, I^2 = 10%, Z = 1.69 [p = 0.09]), dizziness (n = 3 RCTs, RR 11.83, 95% CI, 1.56 to 89.43, I^2 = 0%, Z = 2.39 [p = 0.02]) and enuresis (n = 2 RCTs, RR 4.32, 95% CI, 1.14 to 16.41, I^2 = 52%, Z = 2.15 [p = 0.03]).

- **Authors' conclusion:**
  - Patients with narcolepsy on sodium oxybate showed a significant reduction in cataplexy based on diaries and significant improvement in EDS based on objective (MWT) and validated subjective (ESS) assessment methods. Sodium oxybate was well tolerated in patients with narcolepsy, and most AEs were mild to moderate in severity.
- **Study Appraisal:**
  - **Study sponsorship:**
    - This was not an industry supported study. The authors declared no financial conflicts of interest.
  - **Study rating:**
    - N/A
  - **Study strengths:**
    - All meta-analyses had minimal statistical heterogeneity (p > 0.1).
  - **Study limitations:**
    - The included trials had small sample sizes.
    - Due to the short study durations, long-term efficacy and safety could not be assessed.
    - Publication bias could not be assessed because there were too few trials in the meta-analysis.
    - In the pivotal trials of sodium oxybate, the majority of patients (80 to 85%) were receiving concomitant CNS stimulants. The high percentages of concomitant stimulant use make it impossible to assess the efficacy and safety of sodium oxybate independent of stimulant use (*Xyrem prescribing information 2018*).

Narcolepsy

Study 14. Black & Houghton, *Sleep.* 2006; 29(7):939-946

Study Objective: Evaluate the efficacy of sodium oxybate, modafinil, and the combination of the two for EDS in narcolepsy patients previously taking modafinil	
Study Design, Follow-up	**Treatment Groups** (N = 222 [ITT population])
• DB, PC, PG, MC, RCT • Visit 1: patients were evaluated for trial inclusion (1 to 2 weeks) • Visit 2: occurred 1 to 2 weeks later when overnight PSG was performed followed by the MWT; patients remained on established doses of modafinil and any other concomitant medications (14 ± 4 days) • Visit 3: included baseline PSG and MWT recordings before beginning the treatment phase according to prior DB randomization (28 ± 4 days) • Visit 4: efficacy and safety assessments were performed including PSG and MWT measurements (28 ± 4 days) • Visit 5: final efficacy and safety assessments were performed	• Placebo (n = 55) (Group 1) • Sodium oxybate (n = 50) (Group 2) • Modafinil (n = 63) (Group 3) • Modafinil + sodium oxybate (n = 54) (Group 4) • Patients randomly assigned to Groups 3 and 4 continued to receive their customary doses of modafinil in blinded fashion. Patients randomly assigned to Groups 2 and 4 received sodium oxybate at a dose of 6 g nightly, administered in 2 equally divided doses at bedtime and again 2.5 to 4 hours later for the initial 4-week period of the study. Patients in Groups 1 and 3 received an equivalent volume of placebo sodium-oxybate solution. • Patients returned to the clinic for Visit 4, 4 weeks after efficacy and safety assessments were performed. Patients continued taking modafinil or placebo modafinil at their prescribed dose; however, the dose of sodium oxybate was increased to 9 g nightly in 2 equally divided doses. Patients assigned to placebo sodium oxybate increased their dose of placebo solution by an equivalent volume. All patients continued taking their assigned drug regimen for an additional 4 weeks before returning to the clinic for final efficacy and safety assessments at Visit 5.
Inclusion Criteria	**Exclusion Criteria**
• Age ≥ 18 years • Diagnosis of narcolepsy according to the ICSD criteria • Taking a stimulant medication for the treatment of EDS for ≥ 3 months and taking stable doses of modafinil 200 to 600 mg/day for ≥ 1 month immediately prior to	• Use of sodium oxybate or any investigational therapy within the 30-day period prior to enrollment • Sleep apnea disorder • Any other cause of EDS such as periodic limb movements of sleep (PMLS)

the trial or were taking stable doses of modafinil for ≥ 6 weeks prior to trial entry	• Concurrent use of hypnotics, tranquilizers, sedating antihistamines, benzodiazepines, anticonvulsants, or clonidine • Current or recent history of a substance abuse disorder • Serum creatinine > 2.0 g/dL • Alanine aminotransferase or aspartate aminotransferase > twice the upper limit of normal (ULN) • Bilirubin > 1.5 times the ULN • History of clinically significant dysrhythmia or history of myocardial infarction within the prior 6 months • History of seizure disorder, clinically significant head trauma, or past invasive intracranial surgery • Occupation requiring variable shift work or routine night shifts
Primary Endpoint	**Secondary Endpoints**
• MWT	• ESS • CGI-S • CGI-C

- **Results:**
  - A total of 278 patients were enrolled in the study, of which 231 were randomly assigned to 1 of the 4 treatment groups. The ITT population consisted of 222 patients who received at least 1 dose of DB medication.
  - Compared with the placebo group, the other 3 treatment groups maintained significantly longer mean average daytime sleep latencies after 8 weeks of treatment, as determined by the MWT (Table 8). From the beginning of the baseline period to the end of the DB treatment period, the placebo group demonstrated a significant within-group decrease in sleep latency of 2.72 min as a consequence of withdrawal from modafinil. In contrast, neither the sodium oxybate nor the modafinil groups demonstrated within-group changes in sleep latency at the end of the trial (ie, there were no significant differences between the 2 groups). The mean average sleep latency for both groups was significantly longer than that of placebo-treated patients at the end of the trial. The sodium oxybate/modafinil group demonstrated a mean average sleep latency increase of 2.68 min, compared with baseline, representing the incremental improvement in EDS produced by the addition of sodium oxybate over the response produced by modafinil alone.
  - The sodium oxybate and sodium oxybate/modafinil groups demonstrated significant reductions in ESS scores, compared with placebo at the end of the trial (for each, $p < 0.001$) whereas the scores for the modafinil-treated patients did not significantly change and were not different from the placebo group (Table 9). In the sodium-oxybate group, following the discontinuation of modafinil, the ESS scores decreased from a median average of 15 to 12 by the end of the 8-week DB treatment phase and, similarly, from 15 to 11 in the sodium oxybate/modafinil group (for each, $p < 0.001$ compared with baseline). In contrast, the placebo group demonstrated no change in ESS scores during the same period.

Table 8. Results for MWT[a]

MWT	Placebo (n = 55)	Sodium oxybate (n = 50)	Modafinil (n = 63)	Sodium oxybate + modafinil (n = 54)
Visit 3	9.74 ± 6.57 (n = 55)	11.29 ± 6.40 (n = 49)	10.48 ± 6.03 (n = 63)	10.43 ± 6.77 (n = 54)
Visit 5	6.87 ± 6.14 (n = 53)	11.97 ± 7.21 (n = 48)	9.86 ± 5.89 (n = 62)	13.15 ± 6.91 (n = 53)
Change[b]	-2.72 ± 4.54	0.58 ± 5.68	-0.53 ± 4.36	2.68 ± 5.07
p-value[c]	--	< 0.001	0.006	< 0.001

[a]Data are presented as the mean average of 4 trials per patient ± SD, in minutes, LOCF. Visit 3 followed 2 weeks of SB modafinil at previously established doses. Visit 5 followed 4 weeks of placebo or sodium oxybate 9 g nightly and/or modafinil at previously established doses.
[b]Change from Visit 3 to Visit 5
[c]Compared with placebo

Table 9. Results for ESS[a]

ESS	Placebo (n = 55)	Sodium oxybate (n = 50)	Modafinil (n = 63)	Sodium oxybate + modafinil (n = 54)
Visit 3	16.0 (n = 54)	15.0 (n = 48)	14.0 (n = 61)	15.0 (n = 54)

Visit 4	17.0 (n = 53)	13.0 (n = 48)	15.0 (n = 62)	11.5 (n = 50)
p-value	--	< 0.001	0.071	< 0.001
Visit 5	16.0 (n = 53)	12.0 (n = 49)	15.0 (n = 63)	11.0 (n = 53)
p-value	--	< 0.001	0.767	< 0.001

[a]Data are presented as median average, in minutes, LOCF. Visit 3 followed 2 weeks of SB modafinil at previously established doses. Visit 4 followed 4 weeks of placebo or sodium oxybate 6 g nightly and/or modafinil at previously established doses. Visit 5 followed 4 weeks of placebo or sodium oxybate 9 g nightly and/or modafinil at previously established doses. Significance was as compared with placebo.

- The patients in the sodium oxybate and sodium oxybate/modafinil groups had significantly fewer weekly sleep attacks at the end of the trial, as compared with modafinil and placebo groups. In the sodium oxybate group, sleep attacks decreased from a mean of 10.05 at baseline to 7.10 after 8 weeks ($p < 0.001$) and the sodium oxybate-modafinil group demonstrated a decrease from 11.82 to 5.55 ($p < 0.001$). There was no significant difference between the modafinil- and placebo-treated groups.
- The baseline CGI-S assessment indicated that the patients enrolled in the study were considered to be markedly ill despite treatment with modafinil. At the end of the trial, the sodium oxybate group and sodium oxybate-modafinil group each demonstrated overall improvements in their clinical condition, compared with the placebo group ($p = 0.002$ and $p = 0.023$, respectively). In contrast, the placebo and modafinil groups were judged as demonstrating no significant change in disease severity.
- Based on the CGI-C, a significantly higher percentage of patients in the sodium oxybate and sodium oxybate-modafinil groups had a successful treatment response. Compared with the placebo group, 48.0% ($p = 0.002$) of the sodium oxybate group and 46.3% ($p = 0.023$) of the sodium oxybate-modafinil group were judged to be much improved or very much improved, compared with 21.8% of the placebo group and 19% of the modafinil group.
- Compared with the incidence of AEs reported in the sodium oxybate (60%), modafinil (54.0%), or placebo groups (69.6%), a somewhat greater number of AEs were reported in the sodium oxybate-modafinil group (78.9%). Among all patients, the most common TEAEs included headache (15.2%), nausea (11.7%), dizziness (9.1%), nasopharyngitis (6.1%), vomiting (6.1%), and somnolence (5.6%).
- Nausea and vomiting occurred with the highest frequency in the sodium oxybate groups (1.8% for placebo; 21.1% for sodium oxybate; 3.2% for modafinil; 21.1% for sodium oxybate-modafinil), whereas the incidence of dizziness was highest in the sodium oxybate-modafinil group (21.1% vs 5.4% for placebo, 7.3% for sodium oxybate, and 3.2% for modafinil). Statistically significant differences between treatment groups were also noted with respect to tremor (0% for placebo, 5.5% for sodium oxybate, 0% for modafinil, 14.0% for sodium-oxybate-modafinil) and paresthesia (0% for placebo, 7.3% for sodium oxybate, 0% for modafinil, 3.5% for sodium oxybate-placebo), and upper respiratory tract infections, occurring primarily in the placebo group.
- The number of patients who withdrew from the study early was highest in the sodium oxybate-modafinil group (n = 6) compared with sodium oxybate (n = 4), modafinil (n = 2), or placebo groups (n = 1).

- **Authors' conclusion:**
  - Sodium oxybate and modafinil are both effective for treating EDS in narcolepsy, producing additive effects when used together. Sodium oxybate is beneficial as both monotherapy and as adjunctive therapy for the treatment of EDS in narcolepsy.
- **Study Appraisal:**
  - **Study sponsorship:**
    - Orphan Medical Inc.
  - **Study rating:**
    - Fair
  - **Study strengths:**
    - The study used both objective and patient-reported validated outcome measures.
  - **Study limitations:**
    - The trial duration was short.
    - The study population was already being treated with modafinil for 3 months or longer prior to trial entry. Thus, AEs due to modafinil may have been underrepresented in these patients because only patients who were able to tolerate the medication entered the trial.
    - It is unknown whether the patients were partial responders or non-responders to modafinil prior to trial entry.

Study 15. U.S. Xyrem Multicenter Study Group. *Sleep Med*. 2004;5(2):119-123.

- Fifty-five narcoleptic patients with cataplexy who had received continuous treatment with sodium oxybate for a minimum of 6 months (range, 7 to 44 months, mean 21 months) in a long-term, OL sodium oxybate safety trial were enrolled in a DB treatment withdrawal study. Patients were previously stabilized on sodium oxybate using individualized doses providing optimum clinical effect, ranging from 3 to 9 g nightly. A 2-week SB sodium oxybate treatment phase established a baseline for the weekly occurrence of cataplexy. This was followed by a 2-week DB

phase in which patients were randomized to receive unchanged drug therapy (n = 26) or placebo (n = 29). The primary endpoint was the change in the number of weekly cataplexy attacks from the baseline to the DB treatment phase.

- In the sodium oxybate group, there was no median change in the number of cataplexy attacks between the 2-week SB baseline phase and the 2-week DB phase. In contrast, cataplexy attacks increased by a median of 21.0 in the placebo patients during the same 2-week period ($p < 0.001$); median change from baseline was 39.0 for the placebo group and 16.5 for the sodium oxybate group. The mean (SD; range) frequency of weekly cataplexy attacks over the 2-week baseline period increased from 15.8 (39.9; 0 to 197) to 46.4 (73.8; 0 to 250) at the end of the 2-week DB phase for patients receiving placebo; in patients receiving sodium oxybate, the number of cataplexy episodes was 9.9 (21.4; 0 to 93) and 12.8 (33.5; 0 to 158) at the same time points. There was no evidence of rebound cataplexy in patients who were randomized to placebo following long-term use of sodium oxybate.
- During the SB phase of the study, AEs were reported in 17 (31%) patients. During the DB phase, AEs were reported by 12 (22%) patients, including 3 patients in the sodium oxybate group, and 9 in the placebo group. No AE led to discontinuation and none were serious.
- The authors concluded that this controlled trial provides evidence supporting the long-term efficacy of sodium oxybate for the treatment of cataplexy. In contrast with antidepressant drug therapy, there is no evidence of rebound cataplexy upon abrupt discontinuation of treatment.

Pediatric Study

Study 16. Plazzi et al, *Lancet Child Adolesc Health*. 2018;2(7):483-49

Study Objective: Evaluate the safety and efficacy of sodium oxybate oral solution treatment in children and adolescents with narcolepsy with cataplexy	
Study Design, Follow-up	**Treatment Groups** (N = 106)
• DB, PC, RW, MC, OL study • The study took place in 30 sites in 5 countries (U.S., Finland, France, Italy, and the Netherlands) • Randomization was balanced for age group (7 to 11 years and 12 to 17 years), previous sodium oxybate treatment (taking sodium oxybate at study entry and sodium oxybate -naive), and location (U.S. and European Union).	• Sodium oxybate in 2 divided doses (bedtime and 2.5 to 4 hours later) (n = 31) • Placebo (n = 32) • Sodium oxybate-naïve patients underwent a dose titration period of 3 to 10 weeks in which they were titrated to an effective and tolerable (optimal) dose that achieved a state of cataplexy stability. • Once an optimal dose was achieved, patients entered a stable dose period of 2 weeks. • After the screening period, patients who were taking sodium oxybate at study entry did not undergo titration and entered the stable-dose period. • During the stable dose period, sodium oxybate-naive patients remained on their established optimal dose for 2 weeks. • Patients taking sodium oxybate at entry remained on their previously established dose for 3 weeks. Efficacy assessments were based on the last 2 weeks of the stable dose period. Patients treated with stimulants or wake-promoting agents remained on the same dose during the stable-dose and DB treatment periods. • During the DB treatment period, participants randomly assigned to sodium oxybate remained on the dose and regimen used in the stable-dose period and patients randomly assigned to placebo were administered placebo at a volume and regimen equivalent to the dose and regimen of sodium oxybate taken during the stable-dose period.
Inclusion Criteria	**Exclusion Criteria**
• Patients 7 to 16 years of age at screening with primary diagnosis of narcolepsy with cataplexy as defined by either the ICSD-2 or ICSD-3 criteria, either being treated with sodium oxybate or sodium oxybate-naïve at study entry	• Previous use and discontinuation of sodium oxybate because of no efficacy or poor tolerability • Narcolepsy secondary to another medical condition • History of seizure disorder or head trauma associated with loss of consciousness

• History of ≥ 14 cataplexy attacks in a typical 2-week period, and clinically significant EDS before any narcolepsy treatment was required • If currently treated with sodium oxybate, receiving unchanged doses (twice nightly dosing ≤ 9 g/night) of sodium oxybate for at ≥ 2 months prior to screening with reported clinical improvement of cataplexy	• Clinically significant parasomnia disorder • Evidence of sleep-disordered breathing or hypoventilation • Past or current major thought disorder • Current clinically significant depression or suicidal risk • Concomitant use of sedative hypnotic or anxiolytic medications • Medications with anticataplectic effects (eg, SSRIs, or TCAs) were discontinued ≥ 1 month before study screening. Participants entering the study taking stimulant or wake-promoting medications were allowed to continue these medications.
Primary Endpoint	**Secondary Endpoints**
• Change in weekly number of cataplexy attacks from the last 2 weeks of the stable-dose period (baseline) to the 2 weeks of the DB treatment period	• Change in the Epworth Sleepiness Scale for Children and Adolescents (ESS-CHAD) score from the end of the stable dose period to the end of the DB treatment period • CGI-C for cataplexy severity • CGI-C for narcolepsy overall • Change in QoL using SF-10 Health Survey for Children

- **Results:**
  - Two sodium oxybate-naive patients did not take the study drug and discontinued from the titration period. Sixty-seven (91%) of the sodium oxybate-naive patients were titrated to an optimal dose and entered the stable-dose period. Sixty-three patients (the efficacy population) entered the DB treatment period before the protocol amendment that discontinued the placebo group.
  - Baseline demographics were similar between the sodium oxybate and placebo groups. The median age was 12 years (range, 7 to 17); 73 (69%) of the 106 enrolled patients were White and 63 (59%) were male. At study entry, 74 (70%) patients were sodium oxybate-naive, and 32 (30%) patients were treated with sodium oxybate for a median of 12 months (range, 2.0 to 52.0).
  - At study entry, the median ESS-CHAD score was 14 (moderate daytime sleepiness; range, 5 to 22), and 43 (41%) participants had ESS-CHAD scores ≥ 16. Previous stimulant or wake-promoting medications were used by 53 (50%) patients at study entry. Stimulant or wake-promoting medications were taken by 55 (56%) patients during the stable-dose period, and by 53 (56%) patients during the DB treatment period (56% of patients in the placebo group and 55% of patients in the sodium oxybate group). The median dose of sodium oxybate taken during the stable-dose period was 7.0 g per night (range, 3.0 to 9.0 g per night).
  - Results of the preplanned interim analysis of the primary endpoint (n =35) showed that efficacy was achieved ($p = 0.0002$). Results of the full efficacy analysis (n = 63) showed that patients who were withdrawn from sodium oxybate treatment and randomly assigned to placebo during the DB treatment period had a significant increase in the number of weekly cataplexy attacks compared with patients who were randomly assigned to continue treatment with sodium oxybate. The median change from baseline in the weekly number of cataplexy attacks was 12.7 (Q1, Q3 = 3.4, 19.8) for patients randomly assigned to placebo and 0.3 (-1.0, 2.5) for patients randomly assigned to continue treatment with sodium oxybate ($p < 0.0001$). Additionally, patients receiving placebo had an increased number of cataplexy attacks at week 1, which further increased at week 2.
  - Results of the CGI-C showed that patients who received placebo were rated as having worse cataplexy severity than were patients continuing sodium oxybate treatment. The mean change in CGI-C score for cataplexy severity for the placebo group was -1.5 (SD 1.2) vs -0.4 (1.1) for the sodium oxybate group ($p = 0.0006$).
  - The median change from baseline in ESS-CHAD scores was greater in the placebo group (3.0 [Q1, Q3 = 1.0, 5.0]), indicating increased sleepiness, compared with the sodium oxybate group (0.0 [-1.0, 2.0]; $p = 0.0004$).
  - Results of the CGI-C for narcolepsy overall showed a worsening of narcolepsy in patients randomly assigned to placebo ($p = 0.0008$), with 59% as much worse or very much worse, compared with 10% in patients continuing sodium oxybate treatment ($p < 0.0001$).
  - No significant difference was observed on the SF-10.
  - Generally, results of subgroup analyses by age group and by sodium oxybate status at study entry were similar to the primary analyses for weekly cataplexy attacks and CGI-C for cataplexy severity. These results showed an increased change from baseline (last 2 weeks of the stable-dose period) to the DB period in weekly cataplexy attacks and worsening CGI-C scores for cataplexy severity for patients randomly assigned to placebo; however, ESS-CHAD scores were not significantly different between treatments in the younger age group or in patients taking sodium oxybate at study entry.

- Commonly reported (> 5%) AEs were enuresis (15/72 [21%] sodium oxybate-naive patients vs 4/32 [13%] taking sodium oxybate at study entry), nausea (16 [22%] vs 2 [6%]), vomiting (15 [21%] vs 2 [6%]), headache (13 [18%] vs 4 [13%]), decreased weight (11 [15%] vs 1 [3%]), decreased appetite (8 [11%] vs none), nasopharyngitis (7 [10%] vs none), and dizziness (5 [7%] vs 1 [3%]). Two serious AEs (1 event of severe acute psychosis and 1 event of moderate suicidal ideation) were reported, and both were considered to be related to the study drug. There were no reported deaths.

- **Authors' Conclusion:**
  - The study results supported the clinical efficacy of sodium oxybate for the treatment of both EDS and cataplexy in narcolepsy in children. The safety profile of sodium oxybate was consistent with that observed in adult patients.
- **Study Appraisal:**
  - **Study sponsorship:**
    - Jazz Pharmaceuticals
  - **Study rating:**
    - Fair
  - **Study strengths:**
    - Concomitant stimulant or wake-promoting agents were allowed, which could be considered more representative of real-world clinical practice, in which they are commonly prescribed in addition to sodium oxybate.
  - **Study limitations:**
    - Potential participants who had tried and failed on sodium oxybate previously were excluded.
    - Patients with mild cataplexy (< 14 attacks per typical 2-week period) were excluded.
    - There were fewer patients in the younger age group (7 to 11 years) than in the older age group.
    - Efficacy during the DB, RW period might have been underestimated because of the short duration (2 weeks). Findings from subgroup analyses of ESS-CHAD in patients aged 7 to 11 years and taking sodium oxybate at entry were not significant, and there were fewer patients in these groups.
    - Subgroup analyses were limited by the small number of patients completing the DB period.
    - The study was limited to patients with narcolepsy with cataplexy.

Study 17. Xywav dossier 2020 (unpublished)

Study Objective: Evaluate the safety and efficacy of oxybate salts in adults with narcolepsy with cataplexy	
Study Design, Follow-up	**Treatment Groups**
• DB, PC, RW, MC study • The study was conducted in the U.S. and Europe. • The main study consisted of a ≤ 30-day screening period (N = 255); a 12-week, OL, optimized treatment and titration period to transition to oxybate salts from previous medications for the treatment of cataplexy (N = 201); a 2-week stable-dose period (N = 149); a 2-week DB, RW period (N = 136); and a 2-week safety follow-up. • During the screening period, patients were categorized in the following groups based on their medication use for the treatment of cataplexy at study entry: ○ Sodium oxybate only group ○ Sodium oxybate + other anticataplectics group ○ Other anticataplectics group ○ Cataplexy treatment-naïve group	• DB, RW period: ○ Oxybate salts (n = 69) ○ Placebo (n = 67) • Enrolled patients entered the 12-week, OL optimization and titration period and initiated oxybate salts treatment, with dose titration as needed to optimize efficacy and tolerability. ○ Patients treated with sodium oxybate monotherapy or in combination with other anticataplectics at screening were initiated on a g-to-g equivalent dose of oxybate salts and remained on that same dose for the first 2 weeks. ○ Patients naïve to sodium oxybate initiated oxybate salts at 4.5 g/night and titrated to an optimal dose, with a maximal increase of up to 1.5 g/night/week. ○ Patients taking other anticataplectics at study entry, with or without sodium oxybate, continued taking their other anticataplectics for the first 2 weeks, followed by a taper of other anticataplectics until discontinuation by week 10. • The OL optimized treatment and titration period was followed by a 2-week stable-dose period, during which efficacy assessments were performed while each patient received a stable dose of oxybate salts. At the end of the stable-dose period, patients were randomized 1:1 to receive placebo or to continue oxybate salts treatment.

	Randomization was stratified by treatment for cataplexy at study entry.
Inclusion Criteria	**Exclusion Criteria**
• Patients 18 to 70 years of age with a primary diagnosis of narcolepsy with cataplexy meeting ICSD-3 criteria or DSM-5 criteria and currently untreated or treated with or without anticataplectics • History of ≥ 14 cataplexy attacks in a typical 2-week period prior to receiving any narcolepsy treatment • If patients were receiving medication(s) for the treatment of cataplexy at study entry, the medication regimen was to be stable for ≥ 2 months prior to study entry; if patients were taking wake-promoting agents or stimulants at study entry, they had to be taking stable doses for ≥ 2 months prior to study entry and were to remain on the same dose and regimen throughout the duration of the study. • For patients receiving sodium oxybate at study entry, documentation of prior improvement in cataplexy and EDS with sodium oxybate treatment was required.	• Narcolepsy secondary to another medical condition (eg, CNS injury or lesion) • Restless legs syndrome requiring treatment other than iron supplementation • Uncontrolled hyperthyroidism • History of seizures (other than early childhood febrile seizures) • Head trauma associated with loss of consciousness within the past 5 years • Clinically significant parasomnias • Untreated or inadequately treated sleep-disordered breathing, and succinic semialdehyde dehydrogenase deficiency • Major depression • History of psychotic disorders • Treatment with an antidepressant for cataplexy that could not be withdrawn if considered unsafe due to prior history of depression • Positive urine screen for benzodiazepines or drugs of abuse, a positive alcohol test, a history of substance abuse, or unwillingness to refrain from consuming alcohol during the study • Abnormal ECG
Primary Endpoint	**Secondary Endpoints**
• Change in weekly number of cataplexy attacks from the time during the 2 weeks of the stable-dose period to the time during the 2 weeks of the DB, RW period (determined from patient diaries)	• Change in ESS score from the end of the stable-dose period to the end of the DB, RW period • PGI-C • CGI-C • EQ-5D

- **Results:**
  - Efficacy was assessed in 134 patients who received randomized treatment, and safety was assessed in all enrolled patients (N = 201).
  - Enrolled patients were taking a variety of medications for the treatment of cataplexy at study entry: sodium oxybate only (n = 52), sodium oxybate + other anticataplectics (n = 23), other anticataplectics (n = 36), and cataplexy treatment-naïve (n = 90). During the stable-dose period, 38.8% of patients overall were on stimulants/wake-promoting agents, and the use of stimulants/wake-promoting agents was generally similar across participants by treatment at study entry (sodium oxybate only, 44.2%; sodium oxybate + other anticataplectic, 30.4%; non-sodium oxybate anticataplectic, 47.2%; cataplexy treatment-naïve, 36.7%).
  - Of the 201 patients enrolled, 155 completed the OL optimized treatment and titration period and 149 entered the stable-dose period. Discontinuations prior to the stable-dose period (n = 52) were attributed to AEs (n = 19), protocol deviations (n = 11), withdrawal by participant (n = 6), or other reasons (n = 2).
  - Overall, in the safety population, the mean age was 37.2 years and 60.7% of the participants were female. Prior to any narcolepsy treatment, all participants experienced cataplexy (100%) and EDS (100%), and the majority of participants reported experiencing other symptoms of the narcolepsy pentad: disrupted nighttime sleep (63.2%), sleep-related hallucinations (59.7%), and sleep paralysis (59.7%).
  - Prior to randomization, the median (Q1, Q3) number of weekly cataplexy attacks did not differ in patients randomized to placebo (1.1 [0.0, 7.9]) vs those who continued oxybate salts treatment (1.0 [0.0, 4.4]). During the DB, RW period, patients randomized to continue oxybate salts experienced no change (median [IQR], mean [SD]) in the weekly frequency of cataplexy attacks, while patients randomized to discontinue oxybate salts and take placebo experienced an increase in cataplexy attacks (median [Q1, Q3]: 0.0 [-0.5, 1.7], mean [SD]: 0.12 [5.77] vs 2.4 [0.0,11.6], mean [SD]: 11.46 [24.75], respectively; treatment difference, $p < 0.0001$) (Table 10).
  - Prior to randomization, the median (Q1, Q3) ESS score did not differ in oxybate salts-treated patients who were randomized to placebo vs those who continued oxybate salts treatment (13.0 [9.0, 17.0] vs 14.0 [10.0, 19.0],

respectively). At the end of the DB, RW period, the change in median (Q1, Q3) ESS score from baseline for patients randomized to placebo vs oxybate salts was 2.0 (0.0, 5.0) vs 0.0 (-1.0, 1.0), respectively (Table 10).

Table 10. Primary and key secondary endpoints (efficacy population)

Endpoint	Placebo (N = 65)	Oxybate salts (N = 69)
Change in weekly number of cataplexy attacks from SDP to DB, RW period (primary efficacy endpoint)		
Mean (SD)	11.46 (24.751)	0.12 (5.772)
Median	2.35	0.00
Q1, Q3	0.0, 11.61	-0.49, 1.75
Location shift*	-3.308	
95% CI†; p-value‡	-6.044 to -1.500; p < 0.0001	
Change in ESS score from SDP to DB, RW period (key secondary efficacy endpoint)		
Mean (SD)	3.0 (4.68)	0.0 (2.90)
Median	2.0	0.00
Q1, Q3	0.0, 5.0	-1.0, 1.0
Location shift*	0.0, 5.0	
95% CI‡; p-value‡	-4.00 to -1.00; p < 0.0001	

Abbreviation: SDP = stable dose period
*Location shift between 2 treatment groups and asymptotic 95% CI from Hodges-Lehmann estimate (sodium oxybate-placebo).
† From a rank-based ANCOVA model including the change in average weekly number of cataplexy attacks from the 2 weeks of the SDP to the 2 weeks of the DB, RW period as response variable, prior treatment group and study treatment group as fixed effects, and average weekly number of cataplexy attacks during the 2 weeks of the SDP as covariate.
‡ From a rank-based ANCOVA model including the change in ESS total score from the end of the SDP to the end of the DB, RW period as response variable, prior treatment group and study treatment group as fixed effects, and ESS total score at the end of the SDP as covariate.

- The distribution of PGI-C ratings for narcolepsy overall demonstrated that more patients randomized to placebo experienced worsening of symptoms compared with those randomized to continue oxybate salts treatment (nominal p < 0.0001), with a greater percentage of patients randomized to placebo rating their narcolepsy overall as “much worse” or “very much worse” compared with patients randomized to continue oxybate salts treatment (44.6 vs 4.3%; post hoc nominal p < 0.0001). Similarly, the distribution of CGI-C ratings for narcolepsy overall demonstrated worsening in more participants randomized to placebo (nominal p < 0.0001), with a greater percentage of patients randomized to placebo rated by clinicians as “much worse” or “very much worse” compared with the percentage of patients randomized to continue oxybate salts treatment (60.0 vs 5.9%, respectively; post hoc nominal p < 0.0001).
- At least 1 TEAE was reported by 76.1% of patients while receiving oxybate salts. The most common TEAEs were headache (20.4%), nausea (12.9%), and dizziness (10.4%). Worsening cataplexy was reported as a TEAE by 20 (10.0%) patients; 17 of the 20 patients experienced worsening cataplexy during the tapering of other anticataplectics, and 3 were cataplexy treatment-naïve at study entry. The most common TEAEs leading to discontinuation of oxybate salts during the main study were worsening cataplexy (7/201; 3.5%), nausea (3/201; 1.5%), and anxiety, depressed mood, depression, headache, and irritability (each 2/201; 1.0%). Serious AEs were reported by 6 patients during the main study, including 3 during the OL, optimized treatment and titration period, 1 during the stable-dose period, and 2 reported the day after 2 weeks of placebo treatment in the DB, RW period.

- **Conclusion:**
  - The efficacy of oxybate salts for the treatment of cataplexy and EDS in adults with narcolepsy was demonstrated in this PC, DB, RW study. The overall safety profile of oxybate salts was consistent with sodium oxybate.
- **Study Appraisal:**
  - **Study sponsorship:**
    - Jazz Pharmaceuticals
  - **Study rating:**
    - N/A (unpublished)
  - **Study strengths:**
    - Concomitant stimulant or wake-promoting agents were allowed, which could be considered more representative of real-world clinical practice, in which they are commonly prescribed in addition to sodium oxybate.
  - **Study limitations:**
    - The sample size was small.
    - Patients with mild cataplexy (< 14 attacks per 2-week period) were excluded.
    - Efficacy during the DB, RW period might have been underestimated because of the short duration (2 weeks).
    - The study was limited to patients with narcolepsy with cataplexy.

Solriamfetol

Narcolepsy/OSA

Study 18. Thorpy et al, *Ann Neurol.* 2019;85:359-370 (TONES 2)

Study Objective: Evaluate the safety and efficacy of solriamfetol for the treatment of narcolepsy	
Study Design, Follow-up	**Treatment Groups** (N = 239)
• 12-week, Phase 3, DB, PC, PG, MC, RCT • The study was performed at 50 study centers in the U.S. and Canada and 9 centers in Finland, France, Germany, and Italy. • Randomization was stratified on the basis of presence or absence of cataplexy.	• Solriamfetol 75 mg once daily (n = 59) • Solriamfetol 150 mg once daily (n = 55) • Solriamfetol 300 mg once daily (n = 59) • Placebo (n = 58) • Patients who were randomized to the 150 and 300 mg doses received 75 and 150 mg, respectively, on days 1 through 3 of the first week, with the full dose commencing on day 4.
Inclusion Criteria	**Exclusion Criteria**
• Adults, aged 18 to 75 years • Diagnosis of narcolepsy type 1 or type 2 according to the ICSD-3 or DSM-5 criteria ○ The DSM-5 criteria include patients who have been diagnosed with narcolepsy based on the presence of cataplexy and were applied in this study to include such patients who had been diagnosed with narcolepsy on the basis of cataplexy under ICSD-2 but who no longer meet diagnostic criteria based on a history of cataplexy under ICSD-3. • Baseline mean sleep latency < 25 minutes on the first 4 trials of a 5-trial, 40-minute MWT, baseline ESS score ≥ 10, usual nightly total sleep time ≥ 6 hours (by self-report), and a body mass index (BMI) between 18 and 45 kg/m^2	• Presence of any clinically relevant untreated medical, psychiatric, or behavioral disorder or medical condition other than narcolepsy that is associated with EDS (ie, night-time or variable shift work) • History or presence of any acutely unstable medical or psychiatric disorder, or surgical history that could affect the safety of the patient • Use of medications that could affect the evaluation of EDS or cataplexy unless prior use had stopped for > 5 half-lives of the drug and the patient had returned to baseline level of daytime sleepiness ≥ 7 days prior to the baseline visit.
Co-Primary Endpoints	**Secondary Endpoints**
• Change from baseline to week 12 in: ○ MWT mean sleep latency on the first 4 trials of the MWT ○ ESS score (see Appendix D)	• Percentage of patients who reported improvement on the PGI-C at week 12 • Change in sleep latency on each of the 5 MWT trials • Change in mean sleep latency from baseline to week 4 • Change in ESS from baseline to weeks 1, 4, and 8 • Percentage of patients who reported improvement on the PGI-C at weeks 1, 4, and 8 • Percentage of patients who reported improved at weeks 1, 4, 8, and 12 on the CGI-C • Change in the mean and median weekly number of cataplexy attacks was an exploratory endpoint among the subgroup of patients who reported the presence of cataplexy (assessed by patient diary).

- **Results:**
  - Demographic and clinical characteristics were similar across treatment groups.
  - Overall, the majority of patients (64.4%) were rated by clinicians as moderately or markedly ill and were characterized by impaired wakefulness and EDS, as indicated by baseline MWT mean sleep latency of 7.5 (SD = 5.7) min and ESS scores of 17.2 (SD = 3.2), respectively. Most patients (90.7%) had prior use of psychostimulants; prior use of sodium oxybate and antidepressants was reported for 25.8% and 34.7% of patients, respectively. Cataplexy was present in 50.8% of patients overall, with similar percentages of patients with cataplexy in each of the treatment groups.
  - The mITT population consisted of 231 patients; 1 patient randomized to placebo and 4 patients randomized to solriamfetol 150 mg did not have baseline or at least 1 post-baseline efficacy assessment of MWT and ESS.

- The discontinuation rate was highest in the solriamfetol 300 mg group (27.1%, with lack of efficacy [10.2%, n = 6] and AEs [8.5%, n = 5] as the most common reasons for discontinuation), followed by the solriamfetol 75 mg (16.9%), placebo (10.3%), and solriamfetol 150 mg (7.3%) groups.
- Solriamfetol 300 mg and 150 mg doses met the co-primary endpoints of MWT and ESS as well as the percentage of patients who reported improvement on the PGI-C (all $p < 0.0001$, Table 10). Significance was not achieved for the 75 mg dose on the MWT.
- The LS mean change from baseline at week 12 on the MWT showed an increase in mean sleep latency of 12.3 (SE = 1.4) and 9.8 (SE = 1.3) min with solriamfetol 300 mg and 150 mg, respectively, which was significant compared with 2.1 (SE = 1.3) min for placebo (both $p < 0.0001$).
- For the ESS score, the LS mean change from baseline at week 12 was -6.4 (SE = 0.7), -5.4 (SE = 0.7), and -3.8 (SE = 0.7) for the 300 mg, 150 mg, and 75 mg doses of solriamfetol, respectively, and -1.6 (SE = 0.7) with placebo.
- Improvements were observed at all solriamfetol doses at week 1 on the MWT. The magnitude of effect remained stable over the 12 weeks of the study, and the 300 and 150 mg doses differed from placebo at weeks 1 and 4. Similar patterns were observed on the ESS, with reductions in ESS score relative to placebo observed as early as week 1 with the 300 and 150 mg doses, and effects remained stable over the study duration.
- Evaluation of mean sleep latency on each of the 5 individual MWT trials at week 12 showed efficacy beginning at 1 hour after dosing through 9 hours after dosing for solriamfetol 150 and 300 mg.
- Solriamfetol increased the percentage of patients who reported improvement in their overall condition on the PGI-C. At week 12, these increases were dose-dependent and were significant for the solriamfetol 300 mg (84.7%) and 150 mg (78.2%) doses vs placebo (39.7%; both $p < 0.0001$); the 75 mg dose was nominally significant (67.8%) compared with placebo ($p = 0.0023$, but the comparison was below the hierarchical break). Effects were observed at all doses by week 1 and remained stable over the course of the study.
- On the CGI-C, all doses of solriamfetol resulted in higher percentages of patients who improved as early as week 1, with effects at 300 mg and 150 mg maintained over the study. The results of each of the sensitivity analyses across each of the endpoints (MWT, ESS, and PGI-C) yielded similar results and conclusions as the primary analyses of those endpoints.
- There was no clear effect of solriamfetol on the number of cataplexy attacks per week among patients with cataplexy, although this study was not powered or designed to rigorously evaluate the effects of solriamfetol on cataplexy (data not shown).

Table 11. Hierarchical testing of co-primary and key secondary efficacy endpoints in the mITT population

Endpoint	Solriamfetol treatment difference from placebo, LS mean (95% CI)		
	300 mg	150 mg	75 mg
MWT, min	10.14 (6.39 to 13.90) p < 0.0001	7.65 (3.99 to 11.31) p < 0.0001	2.62 (-1.04 to 6.28) p = 0.1595
ESS	-4.7 (-6.6 to -2.9) p < 0.0001	-3.8 (-5.6 to -2.0) p < 0.0001	-2.2 (-4.0 to -0.3) p = 0.0211
PGI-C, %	45.1 (29.51 to 60.67) p < 0.0001	38.5 (21.86 to 55.19) p < 0.0001	28.1 (10.80 to 45.48) p = 0.0023*

A fixed hierarchical testing procedure was used to correct for multiplicity, starting with the highest solriamfetol dose for the co-primary endpoints and followed by the key secondary endpoint; testing proceeded in that order for each subsequent lower dose, with statistical significance claimed only for those outcomes above the break in the hierarchy.
*Nominal p-value, because it is below the hierarchical break.

- Discontinuations due to AEs occurred in 8.5%, 5.1%, and 1.7% of the solriamfetol 300 mg, 150 mg, and placebo groups, respectively. Other than cataplexy, which resulted in discontinuation in 2 patients, none of the AEs leading to study discontinuation occurred in > 1 patient.
- AEs with an incidence ≥ 5% in the combined solriamfetol dose groups included headache (21.5%), nausea (10.7%), decreased appetite (10.7%), nasopharyngitis (9.0%), dry mouth (7.3%), and anxiety (5.1%).
- No patient had a TEAE of hypertension, and 2 patients had a TEAE of BP increase (1 in the 150 mg group and 1 in the 300 mg group).

- **Authors' conclusion:**
  - Once-daily oral dosing of solriamfetol 150 and 300 mg resulted in major improvements in wakefulness and reductions in EDS associated with narcolepsy together with patient- and clinician-reported global improvements. These results demonstrate that solriamfetol represents an important potential future therapeutic option for the treatment of impaired wakefulness and EDS in individuals with narcolepsy.
- **Study Appraisal:**
  - **Study sponsorship:**
    - Jazz Pharmaceuticals

- **Study rating:**
  - Fair
- **Study strengths:**
  - The study used both objective and patient-reported validated outcome measures.
- **Study limitations:**
  - The trial had a short duration of 12 weeks.
  - Conclusions with regard to the effect of solriamfetol on cataplexy are limited by this study not being designed to rigorously evaluate effects on cataplexy. The frequency of type 2 narcolepsy (ie, without cataplexy) in approximately 50% of the study population was also somewhat higher than reported in the narcolepsy literature.
  - The study did not include modafinil or armodafinil as a comparator.

Study 19. Schweitzer et al, *Am J Respir Crit Care Med.* 2019; 199(11):1421-1431 (TONES 3)

Study Objective: Evaluate the safety and efficacy of solriamfetol for the treatment of EDS in patients with OSA with current or prior sleep apnea treatment	
Study Design, Follow-up	**Treatment Groups** (N = 476)
• 12-week, Phase 3, DB, PC, PG, MC, RCT • The study was conducted at 59 sites in the U.S., Canada, France, Germany, and the Netherlands • Randomization was stratified by adherence or non-adherence to primary OSA therapy, with adherence defined as use ≥ 4 hours per night on ≥ 70% of nights for devices from which hourly usage data could be extracted; use ≥ 70% of nights by daily diary for devices for which usage data could not be retrieved; or history of a surgical intervention for OSA. • Non-adherence was defined as usage of a primary therapy at a level that did not meet the above criteria, ie, non-use of a primary OSA therapy, or a history of a surgical intervention for OSA that was deemed by the investigator to no longer be effective at treating the obstruction.	• Solriamfetol 37.5 mg once daily (n = 58) • Solriamfetol 75 mg once daily (n = 62) • Solriamfetol 150 mg once daily (n = 117) • Solriamfetol 300 mg once daily (n = 118) • Placebo (n = 119) • Patients randomized to the 150 and 300 mg doses received 75 and 150 mg, respectively, on days 1 to 3, with the full dose commencing on day 4.
Inclusion Criteria	**Exclusion Criteria**
• Adults, aged 18 to 75 years • Diagnosis of OSA according to ICSD-3 criteria • Current or prior use of a primary OSA therapy including PAP, mandibular advancement device, or surgical intervention ○ Patients without current primary OSA therapy use or a history of a surgical intervention to treat the underlying obstruction were required to have tried to use a primary OSA therapy for at least 1 month with at least 1 documented adjustment to the therapy (eg, change in PAP pressure, change in mask, change in modality). • Baseline ESS score ≥ 10 • Baseline sleep latency < 30 min for the average of the first 4 of a 5-trial, 40-min MWT • Usual nightly sleep time of ≥ 6 hours	• Usual bedtime later than 1:00 AM • Occupation requiring nighttime shift work or variable shift work • Use of any OTC or prescription medications that could affect the evaluation of EDS; current or past (within the past 2 years) diagnosis of a moderate or severe substance use disorder according to DSM-5 criteria • Nicotine dependence that has an effect on sleep (eg, a patient who routinely awakens at night to smoke) • Any other clinically relevant medical, behavioral, or psychiatric disorder other than OSA that is associated with excessive sleepiness
Co-Primary Endpoints	**Secondary Endpoints**

• Change from baseline to week 12 in:
  ○ Mean sleep latency derived from the first 4 trials of a 5-trial, 40-min MWT
  ○ ESS score
	• Change from baseline to week 12 in sleep latency for each of the 5 individual MWT trials was tested as a pre-specified secondary endpoint for doses that were positive on both co-primary efficacy endpoints
	• Percentage of patients reporting any improvement in PGI-C at week 12

	• Percentage of patients reporting any improvement in CGI-C at week 12

- **Results:**
  - Of the 474 patients who were randomized and took at least 1 dose of study drug, representing the safety population, 404 (85.2%) completed the study.
  - Baseline demographic and clinical characteristics of the safety population were similar across treatments.
  - A history of a surgical intervention for OSA was reported in 17.6% and 13.5% of patients on placebo and solriamfetol, respectively. At baseline, primary OSA therapy was used by 69.7% of patients on placebo and 73.5% of patients on solriamfetol; of these patients, 91.6% on placebo and 92.7% on solriamfetol were using PAP, 2.4% on placebo and 1.1% on solriamfetol were using another type of device as a primary OSA therapy, and in 6.0% of patients on placebo and 6.1% on solriamfetol, the type of primary OSA therapy was not specified.
  - In the 5 treatment groups, from 69.0 to 72.9% of patients were adherent to primary OSA therapy at baseline and from 27.1 to 31.6% were non-adherent.
  - AEs were the most common reason overall for withdrawal (5.1%).
  - Those who successfully completed at least 1 follow-up visit (mITT population) comprised 459 participants.
  - Mean treatment compliance with study drug was 97.2%.
  - The co-primary endpoints of change from baseline at week 12 in MWT and ESS were met at all solriamfetol doses, and the key secondary endpoint of PGI-C was met at all doses except the 37.5 mg dose (Table 12).
    - Solriamfetol resulted in dose-dependent increases in MWT sleep latency at week 1, with LS mean changes from baseline that ranged from 4.2 to 13.3 min for the 37.5 and 300 mg doses, respectively, and that were > placebo (0.4 min). These increases were maintained across the 12 weeks of the study, and all solriamfetol doses resulted in improvements relative to placebo at weeks 4 and 12 ($p < 0.05$). At week 12, effect sizes (Cohen's d) were 0.4, 0.9, 1.1 and 1.2 for solriamfetol 37.5, 75, 150, and 300 mg, respectively. The LS mean change from baseline exceeded 10 min at all time points with solriamfetol 150 mg (11.0 to 12.2 min) and 300 mg (13.0 to 13.8 min), whereas placebo ranged from 0.2 to 1.2 min.
  - Solriamfetol treatment resulted in dose-dependent decreases in ESS score relative to placebo at week 1 that remained stable over the 12-week study duration. These decreases were greater than placebo for all doses at all time points except for the 37.5 mg dose at week 8. Effect sizes at week 12 were 0.4, 0.4, 1.0, and 1.0 for solriamfetol 37.5, 75, 150, and 300 mg, respectively. ESS scores decreased by > 7 points with the 150 and 300 mg doses at week 12 ($p < 0.0001$), whereas placebo decreased by 3.3 points.
  - Change from baseline in sleep latency on each of the 5 individual MWT trials at week 12 was significantly greater with solriamfetol 75, 150, and 300 mg doses compared with placebo, demonstrating efficacy of solriamfetol from 1 to 9 hours after dosing. The 37.5 mg dose showed a significant difference relative to placebo for trial 2 only, based on the pre-specified testing sequence.
  - At week 12, significantly higher percentages of patients on solriamfetol 75 mg (72.4%; $p < 0.05$), 150 mg (89.7%; $p < 0.0001$), and 300 mg (88.7%; $p < 0.0001$) reported overall improvement on the PGI-C relative to placebo (49.1%). These effects were dose-dependent and apparent as early as week 1. Results were generally similar on the CGI-C.
  - There were no meaningful differences in response to solriamfetol between the subgroups of patients who were adherent or non-adherent to primary OSA therapy (data not shown).

Table 12. Hierarchical testing at week 12 of co-primary and key secondary endpoints in the mITT population*

Endpoint	Difference from placebo (95% CI); p-value			
	300 mg	150 mg	75 mg	37.5 mg
MWT, LS mean difference	12.8 (10.0 to 15.6); < 0.0001	10.7 (8.1 to 13.4); < 0.0001	8.9 (5.6 to 12.1); < 0.0001	4.5 (1.2 to 7.9); 0.0086
ESS, LS mean difference	-4.7 (-5.9 to -3.4); < 0.0001	-4.5 (-5.7 to -3.2); < 0.0001	-1.7 (-3.2 to -0.2); 0.0233	-1.9 (-3.4 to -0.3); 0.0161
PGI-C, % difference	39.6 (28.7, to 50.4); < 0.0001	40.5 (29.8 to 51.3); < 0.0001	23.3 (8.6 to 38.0); 0.0035	6.2 (-9.7 to 22.2); 0.4447

*A fixed hierarchical testing procedure was used to correct for multiplicity, starting with the highest solriamfetol dose for the co-primary endpoints and followed by the key secondary endpoint; testing proceeded in that order for each subsequent lower dose, with statistical significance claimed only for those outcomes above the break in the hierarchy.

  - A higher percentage of participants (7.3%) receiving solriamfetol withdrew due to AEs compared with placebo (3.4%). AEs leading to study discontinuation in ≥ 3 patients who received solriamfetol were anxiety (n = 4), feeling jittery (n = 4), nausea (n = 3), dizziness (n = 3), and chest discomfort (n = 3).
  - In most patients, AEs were of mild or moderate severity in the placebo (93.0%) and solriamfetol (94.6%) groups.

- The most frequently reported AEs with solriamfetol, defined as occurring in ≥ 5% of participants in any treatment group, included headache (10.1%), nausea (7.9%), decreased appetite (7.6%), anxiety (7.0%), and nasopharyngitis (5.1%); most of these AEs were dose-dependent.
- Insomnia was reported in 2 patients receiving placebo (1.7%), and in 1 (1.7%), 0 (0%), 3 (2.6%), and 11 (9.3%) participants receiving solriamfetol 37.5, 75, 150, and 300 mg, respectively.
- At week 12, vital signs taken at 7 time points during the day from pre-dose to 9 hours post-dose showed small mean (95% CI) increases from baseline in BP, with the highest at the 300 mg dose of solriamfetol (2.5 [95% CI, 0.4 to 4.6] and 1.5 [0.3 to 2.7] mm Hg for systolic and diastolic, respectively) relative to minimal changes with placebo (-0.2 [95% CI, -1.7 to 1.4] mm Hg systolic; 0.0 [95% CI, -0.9 to 1.0] mm Hg diastolic). Small dose-dependent mean effects were observed on heart rate with solriamfetol 150 and 300 mg (increases of 2.2 [95% CI, 1.0 to 3.4] and 2.9 [95% CI, 1.7 to 4.1] bpm, respectively, relative to 0.1 [95% CI, -0.9 to 1.1] bpm with placebo). No apparent effects of solriamfetol on BP or heart rate were observed on predose vital sign measures at week 12.

- **Authors' conclusion:**
  - Solriamfetol 75, 150, and 300 mg resulted in objective improvements in wakefulness, subjective improvements in sleepiness, and global improvements as evaluated by participants and clinicians. The safety and tolerability profile was consistent with prior studies of solriamfetol in individuals with narcolepsy, and similar to other wake-promoting agents used in the treatment of EDS in OSA.
- **Study Appraisal:**
  - **Study sponsorship:**
    - Jazz Pharmaceuticals
  - **Study rating:**
    - Fair
  - **Study strengths:**
    - The study used both objective and patient-reported validated outcome measures.
    - Participants who were non-adherent to OSA therapy were included in order to study a population more representative of OSA patients in the clinical setting.
  - **Study limitations:**
    - The trial had a short duration of 12 weeks and did not assess longer-term outcomes related to safety and efficacy, including potential long-term CV consequences.
    - The study did not include modafinil or armodafinil as a comparator.

Study 20. Strollo et al, *Chest.* 2019; 155(2):364-374 (TONES 4)

Study Objective: Evaluate the maintenance of efficacy and safety of solriamfetol vs placebo for the treatment of EDS in adults with OSA	
Study Design, Follow-up	**Treatment Groups** (N = 124)
• Phase 3, DB, PC, PG, MC, RW study • After 2 weeks of clinical titration (n = 174, 75 mg once daily starting dose, titrated up or down every 3 days to 75, 150, or 300 mg) and 2 weeks of stable dose administration (n = 148), patients who reported much or very much improvement on the PGI-C and had numerical improvements on the MWT and ESS were randomly assigned to placebo or solriamfetol for 2 additional weeks. • Randomization was stratified by patients' adherence or non-adherence to a primary OSA therapy	• Solriamfetol once daily (n = 62) • Placebo (n = 62)
Inclusion Criteria	**Exclusion Criteria**
• Adults, aged 18 to 75 years • Diagnosis of OSA according to ICSD-3 criteria • Current or primary OSA therapy including CPAP, oral appliance, or surgical intervention • BMI 18 to < 45 kg/m^2 • Baseline ESS score ≥ 10 • Mean sleep latency < 30 minutes on the first 4 trials of a 5-trial, 40-min MWT • Usual nightly sleep time ≥ 6 hours	• Any disorder other than OSA associated with EDS • An occupation requiring nighttime shift work or variable shift work • Excessive caffeine use 1 week prior to the study or nicotine dependence with a reported effect on sleep • Presence of any acutely unstable medical condition, behavioral or psychiatric disorder, or surgical history that could affect patient safety or interfere with study assessments

	• Use of any OTC or prescription medications that could affect EDS evaluation within a period corresponding to at least 5 half-lives of the drug
Co-Primary Endpoints	**Secondary Endpoints**
• Changes from week 4 to week 6 in: ○ MWT mean sleep latency ○ ESS score	• Percentage of patients who reported worsening of their condition on the PGI-C from week 4 to week 6 • Percentage of patients who reported worsening of their condition on the CGI-C from week 4 to week 6 • FOSQ-10

- **Results:**
  - Of 174 patients enrolled into the titration phase, 71% (n = 124) were randomly assigned to placebo or solriamfetol in the DB RW phase. There were 17 study discontinuations (10%) during the titration phase, 6 of which were due to AEs. During the stable dose phase (n = 157), 9 patients (6%) discontinued, and 24 did not enter the RW phase, of whom 21 (13%) were for not meeting the criteria for improvement. Two patients randomly assigned to solriamfetol discontinued during the RW phase; the final mITT population consisted of 62 patients randomly assigned to placebo and 60 to solriamfetol.
  - In the stable dose phase, 14.6%, 31.8%, and 53.5% of patients received the 75, 150, and 300 mg doses of solriamfetol, respectively. Of the 62 patients randomly assigned to solriamfetol in the RW phase, 14.5%, 41.9%, and 43.5% received 75, 150, and 300 mg, respectively.
  - Analyses were performed on the mITT population, defined as patients who were randomly assigned who received ≥ 1 dose of study medication and who had an MWT or ESS assessment at week 4 and ≥ 1 assessment after week 4.
  - Baseline characteristics of the safety population (patients who received ≥ 1 dose of solriamfetol in the titration phase) and the mITT population were comparable between groups.
  - In the titration phase, 65.5% of patients were classified as moderately or markedly ill by their physicians on the CGI-C, 61.5% were male with a mean BMI of 33.3 kg/m^2, and 71.3% were using a primary OSA therapy at baseline.
  - In the mITT population, from baseline to week 4, mean MWT sleep latencies improved from 12.3 to 13.1 min to 29.0 to 31.7 min, and ESS scores improved from 15.3 to 16.0 to 5.9 to 6.4. Patient-reported EDS decreased from ~15 to 16 to ~6, which is within the normal range.
  - From weeks 4 to 6 (RW phase), solriamfetol-treated patients maintained improvements in MWT and ESS. The LS mean (SE) change in MWT mean sleep latency was -12.1 (1.3) min with placebo compared with -1.0 (1.4) min with solriamfetol; LS mean difference between solriamfetol and placebo was 11.2 minutes (95% CI, 7.8 to14.6; p < 0.0001). The LS mean changes in ESS scores were 4.5 (0.7) and -0.1 (0.7) for placebo and solriamfetol, respectively, resulting in an LS mean difference of -4.6 (95% CI, -6.4 to -2.8; p < 0.0001).
    - MWT and ESS results were similar in the subgroups of patients who were adherent or non-adherent with a primary OSA therapy, with slightly larger MD in the non-adherent subgroup.
  - During the RW phase, a statistically significant 50.0% of patients who were switched to placebo reported worsening on the PGI-C relative to 20.0% who continued using solriamfetol (-30.0; 95% CI, -46.0 to -14.0; p < 0.001). Similarly, 59.0% of patients switched to placebo worsened, as rated by the physicians on the CGI-C, vs 21.7% who continued using solriamfetol (-37.3; 95% CI, -53.50 to -21.19; p < 0.0001).
    - Results on the PGI-C and CGI-C were similar in the subgroups of patients who were adherent or non-adherent with a primary OSA therapy, with slightly larger differences from placebo in the non-adherent subgroup.
  - The FOSQ total score improved from mean baseline scores of 13.5 to 13.7 to mean scores of 17.6 to 17.8 after 4 weeks of treatment. At the end of the RW phase (week 6), mean ±SD FOSQ-10 scores were 16.4 ± 2.9 in the placebo group and 17.4 ± 3.0 with solriamfetol, resulting in LS mean (SE) changes of -1.3 (0.4) and -0.2 (0.4), respectively; the LS mean difference significantly favored solriamfetol (1.2; 95% CI, 0.2 to 2.1; p < 0.05).
  - There were no serious AEs during the study, and all withdrawals due to AEs (3.4%, n = 6) occurred during the titration phase. The most frequent AEs leading to withdrawal were headache and palpitations (each reported for 2 patients). There was a higher incidence of AEs during the titration phase (48.9%) than during the stable dose phase (10.2%) and the incidence of AEs increased by dose. The most common AEs (≥ 5%) during the titration phase included headache, (9.8%), dry mouth (6.9%), nausea (6.9%), dizziness (5.7%), and insomnia (5.7%) and the incidence of these AEs (0.6 to 1.3%) was lower during the stable dose phase.
  - During the RW phase, 29.0% of patients who continued using solriamfetol experienced any AE relative to 9.7% of those switched to placebo. Nasopharyngitis was the most frequent AE (4.8%), and there was no evidence of rebound hypersomnia or withdrawal effects after abrupt discontinuation of solriamfetol in the placebo group.
  - The mean changes in vital signs obtained before administration of the dose to 9 hours after administration of the dose on MWT days, across solriamfetol doses, were small increases from baseline to week 6 in systolic (mean ±SD change of 1.6 ± 8.7 mm Hg) and diastolic (0.8 ± 5.3 mm Hg) BP, as well as heart rate (1.0 ± 6.1 bpm). In the RW

phase, small changes in BP (1.5 ± 7.6 mm Hg for systolic and 0.5 ± 4.3 mm Hg for diastolic) and heart rate (0.2 ± 5.9 bpm) were observed in patients randomly assigned to placebo.

- **Authors' conclusion:**
  - Solriamfetol substantially increased objective wakefulness and decreased subjective EDS, with effects that were maintained in participants who continued using treatment relative to a loss of efficacy among those randomly assigned to placebo. The safety profile was consistent with those of other solriamfetol studies, and abrupt discontinuation was not associated with rebound hypersomnia or withdrawal effects.
- **Study Appraisal:**
  - **Study sponsorship:**
    - Jazz Pharmaceuticals
  - **Study rating:**
    - N/A (RW study)
  - **Study strengths:**
    - Inclusion of non-adherent patients in the study likely reflects the characteristics of the general population of patients with OSA who may benefit from solriamfetol treatment.
  - **Study limitations:**
    - The study had a small sample size.
    - The study had a short duration.
    - The inclusion of a population enriched for treatment response, which, although customary for the RW study design, limits characterization of solriamfetol treatment effects in individuals who did not meet response criteria for random assignment.
    - Approximately 20 to 30% of patients were not using a primary OSA therapy at evaluated time points, which may have caused heterogeneity in treatment response.

Study 21. Malhotra et al, *Sleep*. 2020;43(2); Sunosi dossier 2019 (TONES 5)

Study Objective: Evaluate the long-term safety and maintenance of efficacy of solriamfetol for up to 52 weeks in the treatment of patients with narcolepsy or OSA who completed previous trials of solriamfetol	
Study Design, Follow-up	**Treatment Group**
• Phase 3, OL extension study • A 2-week titration phase was followed by a maintenance phase of up to 50 weeks. After ~6 months of OL treatment with solriamfetol, a subgroup of patients entered a 2-week PC RW phase, and the maintenance phase was resumed after RW phase completion.	• Solriamfetol (Group A, n = 519; Group B, n = 124) • Due to differences in study design as well as variable duration between prior study completion and enrollment in the long-term study, participants were enrolled into one of 2 groups. Group A included participants who completed a Phase 3, 12-week narcolepsy or OSA study, and who immediately enrolled into this long-term study; the study duration in this group was 40 weeks. Group B included participants with narcolepsy or OSA who completed one of the Phase 2 studies (or the 6-week, Phase 3 study and were subsequently enrolled into this long-term study. These participants had a study duration for 52 weeks. • During the 2-week titration phase, participants began with a once-daily dose of 75 mg and could titrate up 1 dose level every 3 days (to 150 mg/d and then a maximum dose of 300 mg/d). Participants were also able to titrate down to 75 or 150 mg at any time. • During the RW phase, patients were randomized either to placebo or to continue solriamfetol at their dose of 75 mg, 150 mg, or 300 mg for 2 weeks. • At the end of the RW phase and for the remainder of the study, participants resumed solriamfetol treatment at the same dose that they had received at the beginning of the RW phase.
Inclusion Criteria	**Exclusion Criteria**
• Patients with narcolepsy or OSA who had completed a prior Phase 2 or Phase 3 study with solriamfetol	• See above parent study descriptions
Primary Endpoint	**Secondary Endpoints**

• Change in ESS score from the beginning to the end of the 2-week RW phase	• PGI-C • CGI-C

- **Results:**
  - The overall safety population in the OL phase consisted of 643 patients (417 [64.9%] with OSA and 226 [35.1%] with narcolepsy). A total of 458 (71%) patients completed the study including 66.4% of narcolepsy participants and 73.9% of OSA participants. Patients were primarily male (52.4%) and White (78.7%), with a mean age of 49.3 years. Comorbid conditions included HTN (37.6%), hyperlipidemia (15.2%), and type 2 diabetes (14.0%). The percentages of participants who were titrated to 75, 150, and 300 mg were 10.0%, 32.2%, and 57.9%, respectively. A total of 282 patients were randomized into the RW phase, of which 280 completed this phase. One hundred-forty-one received placebo and 139 received solriamfetol, which represented the mITT population.
  - At study baseline, primary OSA therapy was used by 71.5% of OSA participants; of these participants, 93.2% were using PAP at entry into this study, 2.3% were using another type of device as a primary OSA therapy (eg, neurostimulator or mandibular advancement device), and 5.4% did not specify the type of primary OSA therapy.
  - Efficacy during the maintenance phase
    - In the overall population, mean ESS scores were 15.9 for group A and 16.2 for group B at baseline of the parent and current study, respectively. At week 2, mean ESS scores decreased to 7.6 for group A and to 7.8 for group B, and these improvements (ie, decrease in mean ESS scores) were maintained throughout the study duration. Similar patterns were observed in the individual narcolepsy and OSA populations.
    - The majority of participants (> 94%) reported improvements on the PGI-C at week 2, and these improvements were maintained at generally similar percentages at each assessment; 87.1 to 90.4% of participants in group A and 86.8 to 96.4% of participants in group B reported improvement on the PGI-C at the final assessment. Sustained improvements from the first assessment at week 2 over the study duration were also reported from the clinician perspective on the CGI-C, with good concordance with the PGI-C for the percentage of participants who improved. Similar patterns were observed in the individual narcolepsy and OSA populations.
  - Efficacy during the RW phase
    - All primary and secondary endpoints were met for the RW phase ($p < 0.0001$) in the mITT population. Participants who received solriamfetol during the RW phase maintained their improvement from the beginning of the RW phase, whereas those who were randomized to receive placebo worsened. The LS mean change (from the beginning to the end of the RW phase) for the ESS score was 1.6 with solriamfetol compared with 5.3 with placebo, resulting in an LS mean difference of -3.7 (95% CI, -4.80 to -2.65; $p < 0.0001$. In the overall population, significantly greater percentages of participants in the placebo group worsened during the RW phase compared with the solriamfetol group on both the PGI-C (64.5% vs 28.2%; $p < 0.0001$) and CGI-C (63.8% vs 28.7%; $p < 0.0001$). Similar results were observed by indication across endpoints ($p < 0.05$; data not shown).
  - Over the study duration, 482 participants (75%) had at least 1 TEAE, with similar percentages among those with narcolepsy (74.8%) and OSA (75.1%); 44% of participants (283/643) had a TEAE within the first 2 weeks whereas 12.8% had a TEAE during the second 2 weeks of treatment.
  - The most frequent TEAEs (≥ 5% in combined solriamfetol groups for any indication) were headache (11%), nausea (8.9%), insomnia (7.9%), nasopharyngitis (8.4%), dry mouth (7.3%), anxiety (7.2%), decreased appetite (5.0%), and upper respiratory tract infection (5.0%); most TEAEs were mild or moderate. With the exception of sinusitis, nasopharyngitis, and upper respiratory tract infection, the most common TEAEs occurred most often during the first 2 weeks of the study. TEAE profiles were similar in participants with OSA and narcolepsy. During the OL period, 59 (9.2%) participants had TEAEs that led to withdrawal from the study. TEAEs leading to withdrawal most frequently occurred in the system organ classes of psychiatric disorders (n = 20; 3.1%), nervous system disorders (n = 13; 2.0%), and gastrointestinal disorders (n = 8; 1.2%).TEAEs that most frequently led to withdrawal were anxiety (*n* = 7; 1.1%), headache (n = 4; 0.6%), insomnia (n = 4; 0.6%), irritability (n = 4; 0.6%), nausea (n = 4; 0.6%), depression (n = 3; 0.3%), and dry mouth (n = 3; 0.3%).
  - Serious TEAEs were reported in 27 patients (4.2%) across all phases, including 21 participants (5.0%) with OSA and 6 participants (2.7%) with narcolepsy. There was 1 death that was considered unrelated to study drug. A total of 9 participants, all with OSA, had CV or potential CV serious TEAEs: 2 participants with atrial fibrillation; 1 each with angina pectoris, chest discomfort, chest pain, noncardiac chest pain, cerebrovascular accident, pulmonary embolism; and 1 patient with acute myocardial infarction discussed previously. Of these serious TEAEs, 2 were deemed by the investigator to be related to study drug administration: atrial fibrillation in a patient whose concomitant medications included 2 types of thyroid medication, and cerebrovascular accident in a patient with a history of HTN.
  - Rebound hypersomnia, as assessed by changes on the ESS, was not observed after abrupt discontinuation of solriamfetol in the RW phase.
  - There was no pattern of withdrawal signs or symptoms based on analysis of AEs that occurred after abrupt discontinuation of long-term exposure to solriamfetol (ie, the placebo group in the RW phase).

- No clinically relevant changes in heart rate (< 1 beat per minute [bpm]) or blood pressure (< 1 mm Hg) were observed at assessed time points in group A (n = 519). However, for group B (n = 124), mean increases from baseline ranged from 1.0 to 4.3 mm Hg for systolic blood pressure, 0.8 to 2.4 mm Hg for diastolic blood pressure, and 0.6 to 4.2 bpm for heart rate across the OL extension (up to 52 weeks); these increases were generally greater for participants with narcolepsy relative to OSA. No apparent trends were observed to suggest that there were long-term increases (ie, worsening) in heart rate or blood pressure over time for participants with narcolepsy or OSA (in both group A and group B).

- **Authors' Conclusion:**
  - The long-term maintenance of efficacy with solriamfetol was demonstrated for the treatment of EDS in patients with narcolepsy or OSA. During the maintenance phase, improvements with solriamfetol were maintained for up to 1 year. The safety profile was consistent with prior PC studies of solriamfetol and there were no safety concerns that emerged with chronic administration of up to 1 year.
- **Study Appraisal:**
  - **Study sponsorship:**
    - Jazz Pharmaceuticals
  - **Study rating:**
    - N/A (OL extension study)
  - **Study strengths:**
    - The study had a large sample size.
    - The study included patients with narcolepsy with and without cataplexy.
    - The study followed patients for up to 1 year.
  - **Study limitations:**
    - There was no placebo group for comparison, nor was solriamfetol compared with other wake-promoting agents.
    - The study did not focus on objective outcome measures such as the MWT, neurocognitive performance, or motor vehicle accident risk due to EDS but rather patient-reported outcomes.

CLINICAL GUIDELINES

AASM practice parameters for the treatment of narcolepsy and other hypersomnias of central origin (*Morgenthaler et al 2007a*) (see Appendix H for grading of evidence definitions)

- Recommendations for treatment of narcolepsy:
  - Most of the agents used to treat excessive sleepiness have little effect on cataplexy or other REM sleep associated symptoms. Conversely, most antidepressants and anticataplectics have little effect on alertness. However, some compounds act on both symptoms. Compounds should be selected depending on the diagnosis and the targeted symptoms. Co-administration of 2 or more classes of compounds may be needed in some patients to adequately address their symptoms.
  - Modafinil is effective for treatment of daytime sleepiness due to narcolepsy (Standard).
  - Sodium oxybate is effective for treatment of cataplexy, daytime sleepiness, and disrupted sleep due to narcolepsy (Standard). Sodium oxybate may be effective for treatment of hypnagogic hallucinations and sleep paralysis (Option).
  - Amphetamine, methamphetamine, dextroamphetamine, and methylphenidate are effective for treatment of daytime sleepiness due to narcolepsy (Guideline).
  - Selegiline may be an effective treatment for cataplexy and daytime sleepiness (Option).
  - Ritanserin (not available in the U.S.) may be effective treatment of daytime sleepiness due to narcolepsy (Option).
  - Scheduled naps can be beneficial to combat sleepiness but seldom suffice as primary therapy for narcolepsy (Guideline).
  - TCAs, SSRIs, venlafaxine, and reboxetine (not available in the U.S.) may be effective treatment for cataplexy (Guideline).
  - TCAs, SSRIs, and venlafaxine may be effective treatment for treatment of sleep paralysis and hypnagogic hallucinations (Option).

AASM practice parameters for the medical therapy of OSA (*Morgenthaler et al 2006*)

- Recommendations for pharmacologic therapy of OSA:
  - Successful dietary weight loss may improve the AHI in obese OSA patients (Guideline).
  - Dietary weight loss should be combined with a primary treatment for OSA (Option).
  - Bariatric surgery may be adjunctive in the treatment of OSA in obese patients (Option).
  - SSRIs are not recommended for treatment of OSA (Standard).
  - Protriptyline is not recommended as a primary treatment for OSA (Guideline).
  - Methylxanthine derivatives (aminophylline and theophylline) are not recommended for treatment of OSA (Standard).

- Estrogen therapy (estrogen preparations with or without progesterone) is not indicated for the treatment of OSA (Standard).
- Modafinil is recommended for the treatment of residual EDS in OSA patients who have sleepiness despite effective PAP treatment and who are lacking any other identifiable cause for their sleepiness (Standard).

AASM practice parameters for the clinical evaluation and treatment of circadian rhythm sleep disorders (*Morgenthaler et al 2007b*)

- Recommendations for SWD:
  - Planned napping before or during the night shift is indicated to improve alertness and performance among night shift workers (Standard).
  - Timed light exposure in the work environment and light restriction in the morning, when feasible, is indicated to decrease sleepiness and improve alertness during night shift work (Guideline).
  - Administration of melatonin prior to daytime sleep is indicated to promote daytime sleep among night shift workers (Guideline).
  - Hypnotic medications may be used to promote daytime sleep among night shift workers. Carryover of sedation to the nighttime shift with potential adverse consequences for nighttime performance and safety must be considered (Guideline).
  - Modafinil is indicated to enhance alertness during the night shift for SWD (Guideline).
  - Caffeine is indicated to enhance alertness during the night shift for SWD (Option).

EAN. Management of narcolepsy in adults (*Billiard et al 2011)* (see Appendix I for grading of evidence definitions)

- Recommendations for treatment of narcolepsy:
  - EDS and sleep attacks:
    - The first-line pharmacological treatment of EDS and sleep attacks is not unequivocal. When EDS is the most disturbing symptom, modafinil is recommended based on its efficacy, limited AEs, and dosing flexibility. Modafinil can be taken in variable doses from 100 to 400 mg/day, given as 1 dose in the morning or 2 doses, 1 in the morning and 1 early in the afternoon or tailored to individual patient needs.
    - When EDS coexists with cataplexy and poor sleep, sodium oxybate may be given, based on its well-evidenced efficacy on the 3 symptoms. However, this benefit should be balanced with its more delicate manipulation: the dose should be carefully titrated up to an adequate level over several weeks; the drug should not be used in combination with other sedatives, respiratory depressants and muscle relaxants; patient should be monitored for development of sleep-disordered breathing; and its use should be avoided in depressed patients. Sodium oxybate should be given at a starting dose of 4.5 g/night, increasing by increments of 1.5 g at 4-week intervals. AEs may require dose reduction and slow titration. The optimal response on EDS may take as long as 8 to 12 weeks. Supplementation with modafinil is generally more successful than sodium oxybate alone.
    - Methylphenidate may be an option when the response to modafinil is inadequate and sodium oxybate is not recommended. Moreover, the short-acting effect of methylphenidate may be beneficial when modafinil needs to be supplemented at a specific time of the day, or in situations where maximum alertness is required. Methylphenidate LP and mazindol (not available in the U.S.) may be useful in a limited number of cases.
    - Behavioral treatment measures are always advisable. Essentially, the studies available support on a B Level the recommendation to have regular nocturnal sleep times and to take planned naps during the day, as naps temporarily decrease sleep tendency and shorten reaction time. Because of varying performance demands and limitations on work or home times for taking them, naps are best scheduled on a patient-by-patient basis.
  - Cataplexy:
    - Based on several Class I evidence (Level A rating) studies, sodium oxybate is recommended for first-line pharmacological treatment of cataplexy at a starting dose of 4.5 g/night divided into 2 equal doses of 2.25 g/night. The dose may be increased to a maximum of 9 g/night, divided into 2 equal doses of 4.5 g/night, by increments of 1.5 g at 2-week intervals. Special considerations are noted above.
    - Second-line pharmacological treatments are antidepressants. TCAs, particularly clomipramine (10 to 75 mg), are potent anticataplectic drugs. However, they have the disadvantage of anticholinergic AEs. The starting dosage should always be as low as possible. SSRIs are slightly less active but have fewer AEs. The norepinephrine/serotonin reuptake inhibitor venlafaxine is widely used but lacks any published clinical evidence of efficacy. The norepinephrine reuptake inhibitors, such as reboxetine and atomoxetine, also lack published clinical evidence. Given the well-evidenced efficacy of sodium oxybate and antidepressants, the place for other compounds is fairly limited. There is no accepted behavioral treatment of cataplexy.
  - Hallucinations and sleep paralysis:
    - Recommendations are the same as for cataplexy.
  - Poor sleep:

- According to recent studies with sodium oxybate, this agent appears as the most appropriate to treat poor sleep (Level A). Benzodiazepine or non-benzodiazepine hypnotics may be effective in consolidating nocturnal sleep (Level C). Unfortunately, objective evidence is lacking over intermediate or long-term follow-up. The improvement in poor sleep reported by some patients once established on modafinil is noteworthy.

- Associated features:
  - OSA/hypopnea should be treated no differently in narcoleptic patients than the general population, although it has been shown that CPAP does not improve EDS in most narcolepsy patients. There is usually no need to treat PLMS in narcoleptic patients. Antidepressants and psychotherapy should be used in depressed narcoleptic patients (Level C) as in non-narcoleptic depressed patients.

SAFETY

- **Contraindications**
  - Armodafinil/modafinil
    - Known hypersensitivity to armodafinil or modafinil or its inactive ingredients
  - Pitolisant
    - Patients with severe hepatic impairment
      - Pitolisant is extensively metabolized by the liver and there is a significant increase in pitolisant exposure in patients with moderate hepatic impairment.
  - Solriamfetol
    - Concomitant use of MAOIs, or within 14 days following discontinuation of an MAOI because of the risk of hypertensive reaction
  - Sodium oxybate/oxybate salts
    - Concomitant use of sedative hypnotic agents
    - Concomitant use of alcohol
    - Diagnosis of semialdehyde dehydrogenase deficiency, a rare disorder of inborn error of metabolism variably characterized by mental retardation, hypotonia, and ataxia.
- **Warnings/precautions**
  - Armodafinil/modafinil
    - *Serious dermatologic reactions, including SJS and TEN*
      - Serious rash requiring hospitalization and discontinuation of treatment has been reported in association with the use of modafinil/armodafinil.
      - Rare cases of SJS and TEN have been reported in adults and children in worldwide postmarketing experience with armodafinil/modafinil.
      - There are no factors known to predict the risk of occurrence or the severity of rash associated with armodafinil/modafinil.
      - In cases where the time to onset was reported, serious rash occurred 1 day to 2 months after initiation of armodafinil. Nearly all cases of serious rash associated with modafinil occurred within 1 to 5 weeks after treatment initiation. However, isolated cases with either drug have been reported after prolonged treatment (eg, 3 months).
    - *DRESS/multiorgan hypersensitivity*
      - One fatal case of DRESS (also known as multiorgan hypersensitivity) that occurred in close temporal association (3 weeks) with the initiation of armodafinil treatment has been reported in the postmarketing setting. DRESS typically presents with fever, rash, lymphadenopathy, and/or facial swelling in association with other organ system involvement, such as hepatitis, nephritis, hematologic abnormalities, myocarditis, or myositis, sometimes resembling an acute viral infection. In addition, multiorgan hypersensitivity reactions, including at least 1 fatality in postmarketing experience, have occurred in close temporal association (median time to detection 13 days; range, 4 to 33) to the initiation of modafinil. Although there have been a limited number of reports, multiorgan hypersensitivity reactions may result in hospitalization or be life-threatening.
    - *Angioedema and anaphylaxis reactions*
      - Angioedema and hypersensitivity (with rash, dysphagia, and bronchospasm) were observed in patients treated with armodafinil. No such cases were observed in modafinil clinical trials. However, angioedema has been reported in postmarketing experience with modafinil. Patients should be advised to discontinue therapy and immediately report to their physician any signs or symptoms suggesting angioedema or anaphylaxis (eg, swelling of face, eyes, lips, tongue or larynx; difficulty in swallowing or breathing; hoarseness).
    - *Persistent sleepiness*
      - Patients with abnormal levels of sleepiness who take modafinil/armodafinil should be advised that their level of wakefulness may not return to normal. Patients with excessive sleepiness, including those taking modafinil/armodafinil, should be frequently reassessed for their degree of sleepiness and, if appropriate, advised to avoid driving or any other potentially dangerous activity. Prescribers should also be aware that

patients may not acknowledge sleepiness or drowsiness until directly questioned about drowsiness or sleepiness during specific activities.

- *Psychiatric symptoms*
  - Psychiatric AEs have been reported in association with the use of modafinil/armodafinil.
  - Postmarketing AEs associated with the use of modafinil/armodafinil, some of which have resulted in hospitalization, have included mania, delusions, hallucinations, suicidal ideation, and aggression. Many, but not all, patients who developed psychiatric AEs had a prior psychiatric history.
- *Known CV disease*
  - In clinical studies of modafinil, CV AEs, including chest pain, palpitations, dyspnea and transient ischemic T-wave changes on ECG were observed in 3 patients in association with mitral valve prolapse or left ventricular hypertrophy. Use of modafinil/armodafinil is not recommended in patients with a history of left ventricular hypertrophy or in patients with mitral valve prolapse who have experienced the mitral valve prolapse syndrome when previously receiving CNS stimulants.

○ Pitolisant

- Pitolisant prolongs the QT interval. The use of pitolisant should be avoided in patients with known QT prolongation or in combination with other drugs known to prolong QT interval. Pitolisant should also be avoided in patients with a history of cardiac arrhythmias, as well as other circumstances that may increase the risk of the occurrence of torsade de pointes or sudden death including symptomatic bradycardia, hypokalemia or hypomagnesemia, and the presence of congenital prolongation of the QT interval. The risk of QT prolongation may be greater in patients with hepatic or renal impairment due to higher concentrations of pitolisant. Patients with hepatic or renal impairment should be monitored for increased QTc.

○ Sodium oxybates/oxybate salts

- **Boxed warning** (sodium oxybate):
  - CNS depression
    - Xyrem is a CNS depressant, and respiratory depression can occur with sodium oxybate use.
  - Abuse and misuse
    - Sodium oxybate is the sodium salt of GHB. Abuse or misuse of illicit GHB is associated with CNS AEs, including seizure, respiratory depression, decreased consciousness, coma, and death.
- **Boxed warning** (oxybate salts)
  - CNS depression
    - Oxybate salts is a CNS depressant, and respiratory depression can occur with oxybate salts use.
  - Abuse and misuse
    - The active moiety of oxybate salts is GHB. Abuse or misuse of illicit GHB is associated with CNS AEs, including seizure, respiratory depression, decreased consciousness, coma, and death.
- *Respiratory Depression and Sleep-Disordered Breathing*
  - Sodium oxybate may impair respiratory drive, especially in patients with compromised respiratory function. In overdoses, life-threatening respiratory depression has been reported.
  - During PSG, central sleep apnea and oxygen desaturation were observed in pediatric patients with narcolepsy treated with sodium oxybate.
  - Prescribers should be aware that increased central apneas and clinically relevant desaturation events have been observed with sodium oxybate administration in adult and pediatric patients.
- *Depression and suicidality*
  - In adult clinical trials in patients with narcolepsy (n = 781), there were 2 suicides and 2 attempted suicides in patients treated with sodium oxybate, including 3 patients with a previous history of depressive psychiatric disorder. Of the 2 suicides, 1 patient used sodium oxybate in conjunction with other drugs. Sodium oxybate was not involved in the second suicide. AEs of depression were reported by 7% of 781 patients treated with sodium oxybate, with 4 patients (< 1%) discontinuing because of depression. In most cases, no change in sodium oxybate treatment was required.
  - In a controlled adult trial, with patients randomized to fixed doses of 3 g, 6 g, or 9 g per night sodium oxybate or placebo, there was a single event of depression at the 3 g per night dose. In another adult controlled trial, with patients titrated from an initial 4.5 g per night starting dose, the incidences of depression were 1 (1.7%), 1 (1.5%), 2 (3.2%), and 2 (3.6%) for the placebo, 4.5 g, 6 g, and 9 g per night doses, respectively.
  - In the pediatric clinical trial in patients with narcolepsy (n = 104), 1 patient experienced suicidal ideation while taking sodium oxybate.
- *Other Behavioral or Psychiatric Adverse Reactions*
  - During adult clinical trials in patients with narcolepsy, 3% of 781 patients treated with sodium oxybate experienced confusion, with incidence generally increasing with dose.
  - Less than 1% of patients discontinued the drug because of confusion. Confusion was reported at all recommended doses from 6 g to 9 g per night. In a controlled trial in adults where patients were randomized to

fixed total daily doses of 3 g, 6 g, or 9 g per night or placebo, a dose-response relationship for confusion was demonstrated, with 17% of patients at 9 g per night experiencing confusion. In all cases in that controlled trial, the confusion resolved soon after termination of treatment. In Trial 3 where sodium oxybate was titrated from an initial 4.5 g per night dose, there was a single event of confusion in 1 patient at the 9 g per night dose. In the majority of cases in all adult clinical trials in patients with narcolepsy, confusion resolved either soon after termination of dosing or with continued treatment.

- Anxiety occurred in 5.8% of the 874 patients receiving sodium oxybate in adult clinical trials in another population.
- Other neuropsychiatric reactions reported in adult clinical trials in patients with narcolepsy and the post-marketing setting included hallucinations, paranoia, psychosis, aggression, and agitation.
- In the pediatric clinical trial in patients with narcolepsy, neuropsychiatric reactions, including acute psychosis, confusion, and anxiety, were reported while taking sodium oxybate.

▪ *Parasomnias*

- Sleepwalking, defined as confused behavior occurring at night and at times associated with wandering, was reported in 6% of 781 patients with narcolepsy treated with sodium oxybate in adult controlled and long-term OL studies, with < 1% of patients discontinuing due to sleepwalking. Rates of sleepwalking were similar for patients taking placebo and patients taking sodium oxybate in controlled trials. It is unclear if some or all of the reported sleepwalking episodes correspond to true somnambulism, which is a parasomnia occurring during non-REM sleep, or to any other specific medical disorder. Five instances of significant injury or potential injury were associated with sleepwalking during a clinical trial of sodium oxybate in patients with narcolepsy.

▪ *Use in patients sensitive to high sodium intake (sodium oxybate)*

- Sodium oxybate has a high salt content. In patients sensitive to salt intake (eg, those with HF, HTN, or renal impairment), the amount of daily sodium intake in each dose of sodium oxybate should be considered. Table 13 provides the approximate sodium content per sodium oxybate dose.

Table 13. Approximate sodium content per total nightly dose of sodium oxybate

Sodium oxybate dose/per night	Sodium content/total nightly exposure
3 g	550 mg
4.5 g	820 mg
6 g	1100 mg
7.5 g	1400 mg
9 g	1640 mg

○ Solriamfetol

▪ *Blood pressure and heart rate increases*:

- Solriamfetol increases systolic BP, diastolic BP, and heart rate in a dose-dependent fashion.
- Epidemiological data show that chronic elevations in BP increase the risk of major adverse CV events (MACE), including stroke, heart attack, and CV death. The magnitude of the increase in absolute risk is dependent on the increase in BP and the underlying risk of MACE in the population being treated. Many patients with narcolepsy and OSA have multiple risk factors for MACE, including hypertension, diabetes, hyperlipidemia, and high BMI.
- BP should be assessed and controlled before initiation of treatment with solriamfetol. BP should be monitored regularly during treatment. New onset hypertension and exacerbations of pre-existing hypertension should be treated. Caution should be exercised when treating patients at higher risk of MACE, particularly patients with known CV and cerebrovascular disease, pre-existing hypertension, and patients with advanced age. Caution should be used with other drugs that increase BP and heart rate.
- The need for continued treatment should be periodically re-assessed. If a patient experiences increases in BP or heart rate that cannot be managed with dose reduction of solriamfetol or other appropriate medical intervention, drug discontinuation should be considered.
- Patients with moderate or severe renal impairment may be at higher risk of increases in BP and heart rate because of the prolonged half-life of solriamfetol.

▪ *Psychiatric symptoms*:

- Psychiatric AEs have been observed in clinical trials with solriamfetol, including anxiety, insomnia, and irritability.
- Solriamfetol has not been evaluated in patients with psychosis or bipolar disorders. Caution should be exercised when treating patients with solriamfetol who have a history of psychosis or bipolar disorders.
- Patients with moderate or severe renal impairment may be at a higher risk of psychiatric symptoms because of the prolonged half-life of solriamfetol.

- Patients treated with solriamfetol should be observed for the possible emergence or exacerbation of psychiatric symptoms. If psychiatric symptoms develop in association with the administration of solriamfetol, dose reduction or discontinuation of solriamfetol should be considered.

- **Adverse effects**
  - Armodafinil
    - The most common AEs (≥ 5%) vs placebo were headache (17 vs 9%), nausea (7 vs 3%), dizziness (5 vs 2%), and insomnia (5 vs 1%).
    - In PC clinical trials, 44 of the 645 patients (7%) who received armodafinil discontinued due to an AE compared to 16 of the 445 (4%) patients that received placebo. The most frequent reason for discontinuation was headache (1%).
  - Modafinil
    - The most common AEs (≥ 5%) vs placebo were headache (34 vs 23%), nausea (11 vs 3%), nervousness (7 vs 3%), rhinitis (7 vs 6%), diarrhea (6 vs 5%), back pain (6 vs 5%), anxiety (5 vs 1%), insomnia (5 vs 1%), dizziness (5 vs 4%), and dyspepsia (5 vs 4%).
    - In PC clinical trials, 74 of the 934 patients (8%) who received modafinil discontinued due to an AE compared to 3% of patients that received placebo. The most frequent reasons for discontinuation that occurred at a higher rate for modafinil than placebo patients were headache (2%), nausea, anxiety, dizziness, insomnia, chest pain, and nervousness (each < 1%).
  - Pitolisant
    - In the PC clinical trials conducted in patients with narcolepsy with or without cataplexy, the most common AEs (occurring in ≥ 5% of patients and at twice the rate of placebo) with the use of pitolisant were insomnia (6%), nausea (6%), and anxiety (5%).
  - Sodium oxybate
    - The most common AEs in adults (≥ 2% and more frequently than placebo) were nausea (8 to 20% vs 3%), dizziness (9 to 15% vs 4%), vomiting (2 to 11% vs 1%), somnolence (1 to 8% vs 4%), enuresis (3 to 7% vs 1%), and tremor (2 to 5% vs 0%).
    - The overall AE profile in the pediatric clinical trials was similar to that seen in the adult clinical trial program. The most common AEs of sodium oxybate in pediatric patients (≥ 5%) were enuresis (18%), nausea (17%), headache (16%), vomiting (16%), weight decreased (12%), decreased appetite (8%), and dizziness (6%).
    - Of the 398 patients with narcolepsy treated with sodium oxybate, 10.3% of patients discontinued because of AEs compared with 2.8% of patients receiving placebo. The most common AE leading to discontinuation was nausea (2.8%). The majority of AEs leading to discontinuation began during the first few weeks of treatment.
  - Oxybate salts
    - The most common AEs in the adult study (incidence ≥ 5% of oxybate salts-treated patients) were headache, nausea, dizziness, decreased appetite, parasomnia, diarrhea, hyperhidrosis, anxiety, and vomiting.
    - AEs observed in clinical studies with sodium oxybate (≥ 2%), but not in the adult oxybate salts study, and which may be relevant for oxybate salts included pain, feeling drunk, pain in extremity, cataplexy, disturbance in attention, sleep paralysis, and disorientation.
  - Solriamfetol
    - The most common AEs (≥ 5% and greater than placebo) in either the narcolepsy or OSA populations vs placebo were headache (16 vs 7%), nausea (7 vs 4%), decreased appetite (9 vs 1%), insomnia (5 vs 4%), and anxiety (6 vs 1%).
    - In the 12-week PC clinical trials, 11 of the 396 patients (3%) who received solriamfetol discontinued because of an AE compared to 1 of the 226 patients (< 1%) who received placebo. The AEs resulting in discontinuation that occurred in more than 1 solriamfetol-treated patient and at a higher rate than placebo were: anxiety (2/396; < 1%), palpitations (2/396; < 1%), and restlessness (2/396; < 1%).
    - Drug abuse and dependence
      - Abuse
        - Solriamfetol has potential for abuse. Abuse is the intentional non-therapeutic use of a drug, even once, to achieve a desired psychological or physiological effect. The abuse potential of solriamfetol 300 mg, 600 mg, and 1200 mg (2, 3, and 4 times the maximum recommended dose, respectively) was assessed relative to phentermine, 45 mg and 90 mg, (a Schedule IV controlled substance) in a human abuse potential study in individuals (N = 43) experienced with the recreational use of stimulants. Results from this clinical study demonstrated that solriamfetol produced Drug Liking scores similar to or lower than phentermine. In this XO study, elevated mood was reported by 2.4% in the placebo group, 8 to 24% in the solriamfetol group, and 10 to 18% in the phentermine group. A “feeling of relaxation” was reported in 5% of the placebo group, 5 to 19% of the solriamfetol group, and 15 to 20% of the phentermine group (*Carter et al 2018, Solriamfetol prescribing information 2019*).

- Physicians should carefully evaluate patients for a recent history of drug abuse, especially those with a history of stimulant (eg, methylphenidate, amphetamine, or cocaine) or alcohol abuse, and follow such patients closely, observing them for signs of misuse or abuse of solriamfetol (eg, incrementation of doses, drug-seeking behavior).

- Dependence
  - In a long-term safety and maintenance of efficacy study, the effects of abrupt discontinuation of solriamfetol were evaluated following at least 6 months of solriamfetol use in patients with narcolepsy or OSA. The effects of abrupt discontinuation of solriamfetol were also evaluated during the 2-week safety follow-up periods in the Phase 3 studies. There was no evidence that abrupt discontinuation of solriamfetol resulted in a consistent pattern of AEs in individual patients that was suggestive of physical dependence or withdrawal.

- **Drug Interactions**
  - Modafinil/armodafinil
    - *Effects on CYP3A4/5 substrates*
      - The clearance of drugs that are substrates for CYP3A4/5 (eg, steroidal contraceptives, cyclosporine, midazolam, and triazolam) may be increased by modafinil/armodafinil via induction of metabolic enzymes, which results in lower systemic exposure. Dosage adjustment of these drugs should be considered when these drugs are used concomitantly with modafinil/armodafinil.
      - The effectiveness of steroidal contraceptives may be reduced when used with armodafinil/modafinil and for 1 month after discontinuation of therapy. Alternative or concomitant methods of contraception are recommended for patients taking steroidal contraceptives (eg, ethinyl estradiol) when treated concomitantly with modafinil/armodafinil and for 1 month after discontinuation of modafinil/armodafinil treatment.
      - Blood levels of cyclosporine may be reduced when used with modafinil/armodafinil. Monitoring of circulating cyclosporine concentrations and appropriate dosage adjustment for cyclosporine should be considered when used concomitantly with modafinil/armodafinil.
    - *Effects on CYP2C19 substrates*
      - Elimination of drugs that are substrates for CYP2C19 (eg, phenytoin, diazepam, propranolol, omeprazole, and clomipramine) may be prolonged by modafinil/armodafinil via inhibition of metabolic enzymes, with resultant higher systemic exposure. In individuals deficient in the CYP2D6 enzyme, the levels of CYP2D6 substrates which have ancillary routes of elimination through CYP2C19, such as TCAs and SSRIs, may be increased by co-administration of modafinil/armodafinil. Dose adjustments of these drugs and other drugs that are substrates for CYP2C19 may be necessary when used concomitantly with modafinil/armodafinil.
    - *Warfarin*
      - More frequent monitoring of prothrombin times/international normalized ratio (INR) should be considered whenever modafinil/armodafinil is co-administered with warfarin.
    - *MAOIs*
      - Caution should be used when concomitantly administering MAOIs and modafinil/armodafinil.
  - Pitolisant
    - Drugs having clinically important interactions with pitolisant:

Table 14. Clinically significant drug interactions with pitolisant

Effect of Other Drugs on pitolisant	
Strong CYP2D6 Inhibitors	
Clinical implication:	Concomitant administration of pitolisant with strong CYP2D6 inhibitors increases pitolisant exposure by 2.2-fold.
Prevention or management:	Reduce the dose of pitolisant by half.
Examples:	paroxetine, fluoxetine, bupropion
Strong CYP3A4 Inducers	
Clinical implication:	Concomitant use of pitolisant with strong CYP3A4 inducers decreases exposure of pitolisant by 50%.
Prevention or management:	Assess for loss of efficacy after initiation of a strong CYP3A4 inducer. For patients stable on pitolisant 8.9 mg or 17.8 mg once daily, increase the dose of pitolisant to reach double the original daily dose (ie, 17.8 mg or 35.6 mg, respectively) over 7 days. If concomitant dosing of a strong CYP3A4 inducer is discontinued, decrease pitolisant dosage by half.
Examples:	rifampin, carbamazepine, phenytoin
Histamine-1 (H_1) Receptor Antagonists	

Clinical implication:	Pitolisant increases the levels of histamine in the brain; therefore, H_1 receptor antagonists that cross the blood-brain barrier may reduce the effectiveness of pitolisant.
Prevention or management:	Avoid centrally acting H_1 receptor antagonists.
Examples:	pheniramine maleate, diphenhydramine, promethazine (antihistamines) imipramine, clomipramine, mirtazapine (tri or tetracyclic antidepressants)
QT interval prolongation	
Clinical implication:	Concomitant use of drugs that prolong the QT interval may add to the QT effects of pitolisant and increase the risk of cardiac arrhythmia.
Prevention or management:	Avoid the use of pitolisant in combination with other drugs known to prolong the QT interval.
Examples:	Class 1A antiarrhythmics: quinidine, procainamide, disopyramide Class 3 antiarrhythmics: amiodarone, sotalol Antipsychotics: ziprasidone, chlorpromazine, thioridazine Antibiotics: moxifloxacin
Sensitive CYP3A4 Substrates	
Clinical implication:	Pitolisant is a borderline/weak inducer of CYP3A4. Therefore, reduced effectiveness of sensitive CYP3A4 substrates may occur when used concomitantly with pitolisant.
Prevention or management:	The effectiveness of hormonal contraceptives (eg, ethinyl estradiol) may be reduced when used with pitolisant and effectiveness may be reduced for 21 days after discontinuation of therapy.
Examples:	midazolam, hormonal contraceptives, cyclosporine

- Drugs having no clinically important interactions with pitolisant:
  - A clinical study was conducted to evaluate the concomitant use of pitolisant with modafinil or sodium oxybate. This study demonstrated no clinically relevant effect of modafinil or sodium oxybate on the PK of pitolisant and no effect of pitolisant on the PK of modafinil or sodium oxybate.
  - A clinical study showed that strong CYP3A4 inhibitors (eg, ketoconazole, grapefruit juice) have no effect on the PK of pitolisant.

- Sodium oxybate/oxybate salts
  - *Alcohol, sedative hypnotics, and CNS depressants*
    - Sodium oxybate/oxybate salts are contraindicated in combination with alcohol or sedative hypnotics. Use of other CNS depressants may potentiate the CNS-depressant effects of sodium oxybate/oxybate salts.
  - *Divalproex sodium*
    - Concomitant use of sodium oxybate with divalproex sodium results in an increase in systemic exposure to GHB, which was shown to cause a greater impairment on some tests of attention and working memory in a clinical study. A similar increase in exposure is expected with concomitant use of oxybate salts and divalproex sodium; therefore, an initial dose reduction of oxybate salts is recommended when used concomitantly with divalproex sodium. Prescribers are advised to monitor patient response closely and adjust dose accordingly if concomitant use of oxybate salts and divalproex sodium is warranted.
- Solriamfetol
  - *MAOIs*
    - Solriamfetol should not be administered concomitantly with MAOIs or within 14 days after discontinuing MAOI treatment. Concomitant use of MAOIs and noradrenergic drugs may increase the risk of a hypertensive reaction. Potential outcomes include death, stroke, myocardial infarction, aortic dissection, ophthalmological complications, eclampsia, pulmonary edema, and renal failure.
  - *Drugs that increase BP and/or heart rate*
    - Concomitant use of solriamfetol with other drugs that increase BP and/or heart rate has not been evaluated, and such combinations should be used with caution.
  - *Dopaminergic drugs*
    - Dopaminergic drugs that increase levels of dopamine or that bind directly to dopamine receptors might result in pharmacodynamic interactions with solriamfetol. Interactions with dopaminergic drugs have not been evaluated with solriamfetol. Caution should be used when concomitantly administering dopaminergic drugs with solriamfetol.

- **Risk Evaluation and Mitigation Strategy (REMS)**
  - Sodium oxybate/oxybate salts

- Sodium oxybate/oxybate salts are available only through a REMS program called the Xywav and Xyrem REMS program because of the risks of CNS depression and abuse and misuse.
- Notable requirements of the Xywav and Xyrem REMS program include:
  - Healthcare Providers who prescribe Xyrem and Xywav are specially certified.
  - Xywav and Xyrem will be dispensed only by the central pharmacy that is specially certified.
  - Xywav and Xyrem will be dispensed and shipped only to patients who are enrolled in the Xywav and Xyrem REMS Program with documentation of safe use.

DOSAGE AND ADMINISTRATION

- **Armodafinil**
  - Narcolepsy/OSA
    - The recommended dosage of armodafinil for patients with OSA or narcolepsy is 150 mg to 250 mg taken orally once a day as a single dose in the morning.
    - In patients with OSA, doses up to 250 mg/day, given as a single dose, have been well tolerated, but there is no consistent evidence that these doses confer additional benefit beyond that of the 150 mg/day dose.
  - SWD
    - The recommended dosage of armodafinil for patients with SWD is 150 mg taken orally once a day as a single dose approximately 1 hour prior to the start of their work shift.
  - Hepatic impairment
    - The dosage of armodafinil should be reduced in patients with severe hepatic impairment.
- **Modafinil**
  - Narcolepsy/OSA
    - The recommended dosage of modafinil for patients with narcolepsy or OSA is 200 mg taken orally once a day as a single dose in the morning.
  - SWD
    - Doses up to 400 mg/day, given as a single dose, have been well tolerated, but there is no consistent evidence that this dose confers additional benefit beyond that of the 200 mg/day dose.
  - Hepatic impairment
    - In patients with severe hepatic impairment, the dose of modafinil should be reduced to one-half of that recommended for patients with normal hepatic function.
- **Pitolisant**
  - Recommended dosage
    - The recommended dosage of pitolisant is 17.8 to 35.6 mg administered orally once daily in the morning upon wakening. The dose should be titrated as follows:
      - Week 1: Initiate with a dosage of 8.9 mg (two 4.45 mg tablets) once daily
      - Week 2: Increase dosage to 17.8 mg (one 17.8 mg tablet) once daily
      - Week 3: May increase to the maximum recommended dosage of 35.6 mg (two 17.8 mg tablets) once daily
    - Dose may be adjusted based on tolerability.
    - If a dose is missed, patients should take the next dose the following day in the morning upon wakening.
    - It may take up to 8 weeks for some patients to achieve a clinical response.
  - Hepatic impairment
    - In patients with moderate hepatic impairment, pitolisant should be initiated at 8.9 mg once daily and increased after 14 days to a maximum dosage of 17.8 mg once daily.
    - Pitolisant is contraindicated in patients with severe hepatic impairment. Pitolisant has not been studied in patients with severe hepatic impairment.
  - Renal impairment and ESRD
    - In patients with moderate and severe renal impairment, pitolisant should be initiated at 8.9 mg once daily and increased after 7 days to a maximum dosage of 17.8 mg once daily.
    - Pitolisant is not recommended in patients with ESRD.
  - Concomitant use with strong CYP2D6 inhibitors and strong CYP3A4 inducers
    - Coadministration with strong CYP2D6 inhibitors
      - For patients receiving strong CYP2D6 inhibitors, pitolisant should be initiated at 8.9 mg once daily and increased after 7 days to a maximum dosage of 17.8 mg once daily.
      - For patients on a stable dose of pitolisant, the pitolisant dose should be reduced by half upon initiating strong CYP2D6 inhibitors.
    - Coadministration with strong CYP3A4 inducers
      - Concomitant use of pitolisant with strong CYP3A4 inducers decreases pitolisant exposure by 50%.
      - Patients should be assessed for loss of efficacy after initiation of a strong CYP3A4 inducer.

- For patients stable on pitolisant 8.9 mg or 17.8 mg once daily, the dose of pitolisant should be increased to double the original daily dose (ie, 17.8 mg or 35.6 mg, respectively) over 7 days.
- If concomitant dosing of a strong CYP3A4 inducer is discontinued, the pitolisant dosage should be decreased by half.

○ Patients who are known CYP2D6 poor metabolizers
- In patients known to be poor CYP2D6 metabolizers, pitolisant should be initiated at 8.9 mg once daily and titrated to a maximum dose of 17.8 mg once daily after 7 days.

• **Sodium oxybate/oxybate salts**

○ Adult dosing
- The recommended starting dose of sodium oxybate/oxybate salts is 4.5 g per night administered orally, divided into 2 doses: 2.25 g at bedtime and 2.25 g taken 2.5 to 4 hours later (see Table 15). The dosage should be increased by 1.5 g per night at weekly intervals (additional 0.75 g at bedtime and 0.75 g taken 2.5 to 4 hours later) to the effective dosage range of 6 g to 9 g per night orally. Doses higher than 9 g per night have not been studied and should not ordinarily be administered.

Table 15. Recommended adult sodium oxybate/oxybate salts dose regimen

If a patient's total nightly dose is:	Take at bedtime:	Take 2.5 to 4 hours later:
4.5 g	2.25 g	2.25 g
6 g	3 g	3 g
7.5 g	3.75 g	3.75 g
9 g	4.5 g	4.5 g

○ Pediatric dosing
- Sodium oxybate/oxybate salts are administered orally twice nightly. The recommended starting pediatric dosage, titration regimen, and maximum total nightly dosage are based on patient weight, as specified in Table 16. The dosage may be gradually titrated based on efficacy and tolerability.

Table 16. Recommended pediatric sodium oxybate/oxybate salts dosage for patients ≥ 7 years of age*

Patient weight	Initial Dosage		Maximum Weekly Dosage Increase		Maximum Recommended Dosage	
	Take at bedtime:	Take 2.5 to 4 hours later:	Take at bedtime:	Take 2.5 to 4 hours later:	Take at bedtime:	Take 2.5 to 4 hours later:
< 20 kg†	There is insufficient information to provide specific dosing recommendations for patients who weigh < 20 kg.					
20 to < 30 kg	≤ 1 g	≤ 1 g	0.5 g	0.5 g	3 g	3 g
30 to < 45 kg	≤ 1.5 g	≤ 1.5 g	0.5 g	0.5 g	3.75 g	3.75 g
≥ 45 kg	≤ 2.25 g	≤ 2.25 g	0.75 g	0.75 g	4.5 g	4.5 g

*For patients who sleep > 8 hours per night, the first dose may be given at bedtime or after an initial period of sleep.
†In patients ≥ 7 years of age who weigh < 20 kg, a lower starting dosage, lower maximum weekly dosage increases, and lower total maximum nightly dosage should be considered.
Note: Unequal dosages may be required for some patients to achieve optimal treatment.

○ Important administration instructions
- The first dose of sodium oxybate/oxybate salts should be taken at least 2 hours after eating.
- Both doses should be prepared prior to bedtime. Prior to ingestion, each dose should be diluted with approximately one-fourth cup (approximately 60 mL) of water in the empty pharmacy containers provided. Patients should take both doses while in bed and lie down immediately after dosing as oxybate/oxybate salts may cause them to fall asleep abruptly without first feeling drowsy. Patients will often fall asleep within 5 minutes of taking oxybate/oxybate salts, and will usually fall asleep within 15 minutes, though the time it takes any individual patient to fall asleep may vary from night to night. Patients should remain in bed following ingestion of the first and second doses, and should not take the second dose until 2.5 to 4 hours after the first dose. Patients may need to set an alarm to awaken for the second dose. Rarely, patients may take up to 2 hours to fall asleep.
- If the second dose is missed, that dose should be skipped and the drug should not be taken again until the next night. Both doses should never be taken at one time.

○ Patients transitioning from sodium oxybate to oxybate salts
- On the first night of dosing with oxybate salts, treatment should be initiated at the same dose (g for g) and regimen as sodium oxybate. The dose should be titrated as needed based on efficacy and tolerability.

○ Hepatic impairment

- The recommended starting dosage of sodium oxybate/oxybate salts in patients with hepatic impairment is one-half of the original dosage per night administered orally, divided into 2 doses.

- Dose adjustment with co-administration of divalproex sodium
  - When initiating divalproex sodium in patients receiving a stable dosage of sodium oxybate/oxybate salts, a reduction of the sodium oxybate/oxybate salts dosage by at least 20% is recommended with initial concomitant use. When initiating sodium oxybate/oxybate salts in patients already taking divalproex sodium, a lower starting dosage of sodium oxybate/oxybate salts is recommended. Subsequently, the dosage can be adjusted based on individual clinical response and tolerability.

- **Solriamfetol**
  - Solriamfetol should be administered upon awakening with or without food. Patients should avoid taking solriamfetol within 9 hours of planned bedtime because of the potential to interfere with sleep if taken too late in the day.
  - Solriamfetol 75 mg tablets are functionally scored tablets that can be split in half (37.5 mg) at the score line.
  - Narcolepsy
    - Solriamfetol should be initiated at 75 mg once daily in adults with narcolepsy. The recommended dose range is 75 to 150 mg once daily. Based on efficacy and tolerability, the dosage of solriamfetol may be doubled at intervals of at least 3 days. The maximum recommended dose is 150 mg once daily. Dosages above 150 mg daily do not confer increased effectiveness sufficient to outweigh dose-related AEs.
  - OSA
    - Solriamfetol should be initiated at 37.5 mg once daily in adults with OSA. The recommended dosage range is 37.5 to 150 mg once daily. Based on efficacy and tolerability, the dosage of solriamfetol may be doubled at intervals of at least 3 days. The maximum recommended dosage is 150 mg once daily. Dosages above 150 mg daily do not confer increased effectiveness sufficient to outweigh dose-related AEs.
  - Renal impairment
    - Moderate renal impairment (estimated glomerular filtration rate [eGFR] 30 to 59 mL/min/1.73 m^2): dosing should be initiated at 37.5 mg once daily. Based on efficacy and tolerability, the dose may be increased to a maximum of 75 mg once daily after at least 7 days.
    - Severe renal impairment (eGFR 15 to 29 mL/min/1.73 m^2): a dose of 37.5 mg should be administered daily. The maximum recommended dose is 37.5 mg.
    - ESRD (eGFR < 15 mL/min/1.73 m^2): solriamfetol is not recommended for use in patients with ESRD.

SPECIFIC POPULATIONS

- **Geriatrics**
  - Armodafinil
    - In elderly patients, elimination of armodafinil and its metabolites may be reduced as a consequence of aging. Therefore, consideration should be given to the use of lower doses and close monitoring in this population.
  - Modafinil
    - In clinical trials, experience in a limited number of modafinil-treated patients who were > 65 years of age showed an incidence of AEs similar to other age groups. In elderly patients, elimination of modafinil and its metabolites may be reduced as a consequence of aging. Therefore, consideration should be given to the use of lower doses and close monitoring in this population.
  - Pitolisant
    - Limited PK data are available in healthy elderly patients. A PK study that compared 12 elderly patients (68 to 82 years of age) to 12 healthy adults (18 to 45 years of age) did not reveal any significant differences in drug exposure.
    - Of the total number of patients with narcolepsy in clinical studies of pitolisant, 14 patients (5%) were ≥ 65 years of age. No overall differences in safety or effectiveness were observed between these patients and younger patients in these clinical trials, but greater sensitivity of some older individuals cannot be ruled out.
  - Sodium oxybate/oxybate salts
    - Clinical studies of sodium oxybate/oxybate salts in patients with narcolepsy did not include sufficient numbers of patients ≥ 65 years of age to determine whether they respond differently from younger patients. In controlled trials of sodium oxybate in another population, 39 (5%) of 874 patients were ≥ 65 years of age. Discontinuations of treatment due to AEs were increased in the elderly compared to younger adults (20.5% vs 18.9%). Frequency of headaches was markedly increased in the elderly (39% vs 19%). The most common AEs were similar in both age categories.
  - Solriamfetol
    - Of the total number of patients in the narcolepsy and OSA clinical studies treated with solriamfetol, 13% (123/930) were 65 years of age or over.
    - No clinically meaningful differences in safety or efficacy were observed between elderly and younger patients.

- Solriamfetol is predominantly eliminated by the kidney. Because elderly patients are more likely to have decreased renal function, dosing may need to be adjusted based on eGFR in these patients. Consideration should be given to the use of lower doses and close monitoring in this population.

- **Pediatrics**
  - Armodafinil
    - Safety and efficacy in pediatric patients have not been established.
  - Modafinil
    - Safety and efficacy in pediatric patients have not been established.
  - Pitolisant
    - The safety and effectiveness of pitolisant in pediatric patients have not been established.
    - Limited PK data from 24 pediatric patients with narcolepsy (7 to < 18 years of age) receiving a single dose of pitolisant suggested that pediatric patients have higher exposure to pitolisant than adults. The exposure (C_{max} and AUC) of pitolisant was 2-fold higher in pediatric patients 12 to < 18 years and 3-fold higher in pediatric patients 7 to < 12 years compared to adults.
  - Sodium oxybate/oxybate salts
    - The safety and effectiveness of sodium oxybate in the treatment of cataplexy or EDS in pediatric patients ≥ 7 years of age with narcolepsy have been established in a DB, PC, RW study.
    - The safety and effectiveness of oxybate salts for the treatment of cataplexy or EDS in pediatric patients ≥ 7 years of age with narcolepsy have been established. Oxybate salts has not been studied in a pediatric clinical trial. Use of oxybate salts in pediatric patients ≥ 7 years of age with narcolepsy is supported by evidence from the RW study of sodium oxybate, a study in adults showing a treatment effect of oxybate salts similar to that observed with sodium oxybate, PK data of sodium oxybate from adult and pediatric patients, and PK data of oxybate salts from healthy adult volunteers.
    - Safety and effectiveness of sodium oxybate and oxybate salts in pediatric patients < 7 years of age have not been established.
  - Solriamfetol
    - Safety and efficacy in pediatric patients have not been established. Clinical studies of solriamfetol in pediatric patients have not been conducted.
- **Renal dysfunction**
  - Pitolisant
    - The PK of pitolisant in patients with ESRD (eGFR of < 15 mL/minute/1.73 m^2) is unknown.
    - See dosing section above.
  - Solriamfetol
    - See dosing section above.
- **Hepatic dysfunction**
  - Armodafinil
    - See dosing section above.
  - Modafinil
    - See dosing section above.
  - Pitolisant
    - Pitolisant is contraindicated in patients with severe hepatic impairment (Child Pugh C) as it has not been studied in this population. Pitolisant is extensively metabolized by the liver and there is a significant increase in pitolisant exposure in patients with moderate hepatic impairment.
    - See dosing section above for patients with moderate hepatic impairment.
    - Patients with mild hepatic impairment (Child Pugh A) should be monitored. No dosage adjustment of pitolisant is recommended in patients with mild hepatic impairment.
  - Sodium oxybate/oxybate salts
    - See dosing section above.
- **Pregnancy and nursing**
  - Armodafinil
    - There is a pregnancy exposure registry that monitors pregnancy outcomes in women exposed to armodafinil during pregnancy. Healthcare providers are encouraged to register pregnant patients, or pregnant women may enroll themselves in the registry by calling 1-866-404-4106.
    - Limited available data on armodafinil use in pregnant women are insufficient to inform a drug associated risk of adverse pregnancy outcomes.
    - There are no data on the presence of armodafinil or its metabolites in human milk, the effects on the breastfed infant, or the effect of this drug on milk production. Modafinil was present in rat milk when animals were dosed during the lactation period. The developmental and health benefits of breastfeeding should be considered along

with the mother's clinical need for armodafinil and any potential AEs on the breastfed child from armodafinil or from the underlying maternal condition.

- Modafinil
  - A pregnancy registry has been established to collect information on the pregnancy outcomes of women exposed to modafinil. Healthcare providers are encouraged to register pregnant patients, or pregnant women may enroll themselves in the registry by calling 1-866-404-4106.
  - There are no adequate and well-controlled studies of modafinil in pregnant women.
  - It is not known whether modafinil or its metabolites are excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when modafinil is administered to a nursing woman.
  - A pregnancy registry reported an elevated rate of major congenital anomalies (17%) and cardiac anomalies (4%) among women in the U.S. exposed to modafinil and/or armodafinil (some took additional drugs). Based on these data, Health Canada issued a warning that modafinil is contraindicated in women who are pregnant or may become pregnant in June 2019 (*Eichler et al 2019*).
- Pitolisant
  - There is a pregnancy exposure registry that monitors pregnancy outcomes in women who are exposed to pitolisant during pregnancy. Patients should be encouraged to enroll in the pitolisant pregnancy registry if they become pregnant. To enroll or obtain information from the registry, patients can call 1-800-833-7460.
  - Available case reports from clinical trials and postmarketing reports with pitolisant use in pregnant women have not determined a drug-associated risk of major birth defects, miscarriage or adverse maternal or fetal outcomes.
  - There are no data on the presence of pitolisant in human milk, the effects on the breastfed infant, or the effect of this drug on milk production.
  - Pitolisant is present in the milk of lactating rats. When a drug is present in animal milk, it is likely that the drug will be present in human milk. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for pitolisant and any potential AEs on the breastfed child from pitolisant or from the underlying maternal condition.
- Sodium oxybate/oxybate salts
  - There are no adequate data on the developmental risk associated with the use of sodium oxybate or oxybate salts in pregnant women.
  - GHB is excreted in human milk after oral administration of sodium oxybate. There is insufficient information on the risk to a breastfed infant, and there is insufficient information on milk production in nursing mothers. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for sodium oxybate/oxybate salts and any potential AEs on the breastfed infant from sodium oxybate or from the underlying maternal condition.
- Solriamfetol
  - Pregnancy Exposure Registry There is a pregnancy exposure registry that monitors pregnancy outcomes in women exposed to solriamfetol during pregnancy. Healthcare providers are encouraged to register pregnant patients, or pregnant women may enroll themselves in the registry by calling 1-877-283-6220 or contacting the company at *www.SunosiPregnancyRegistry.com*.
  - Available data from case reports are not sufficient to determine drug-associated risks of major birth defects, miscarriage, or adverse maternal or fetal outcomes.
  - There are no data available on the presence of solriamfetol or its metabolites in human milk, the effects on the breastfed infant, or the effect of this drug on milk production.
  - Solriamfetol is present in rat milk. When a drug is present in animal milk, it is likely that the drug will be present in human milk. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for solriamfetol and any potential AEs on the breastfed child from solriamfetol or from the underlying maternal condition.

APPENDICES

Appendix A. Definitions of terms (*Freedman 2019*)

- Epoch: An epoch is a standard 30-second interval of a PSG to which a sleep stage is assigned. In special situations, an epoch can be longer or shorter.
- Sleep onset: The recommended definition for sleep onset for the MWT is 3 consecutive epochs of stage 1 sleep or 1 epoch of any other stage of sleep.
- Sleep latency: Sleep latency is the duration from lights out to the onset of sleep.
- Mean sleep latency: The mean sleep latency is the average of the sleep latencies determined during a test.

Appendix B. Multiple Sleep Latency Test (MSLT) (*American Sleep Association Web site, Thorpy 1992*)

- The MSLT is a diagnostic tool that measures the time it takes an individual to fall asleep in ideal quiet conditions during the day. It objectively measures daytime sleepiness. Colloquially known as the daytime nap study, the MSLT is also a standard tool used to diagnose idiopathic hypersomnia and narcolepsy.
- The MSLT is based on the fact that the more tired an individual is, the faster they will fall asleep. In addition to assessing for narcolepsy and idiopathic hypersomnia, the MSLT is used to evaluate insomnia, OSA, circadian rhythm sleep disorders, and response to treatment following effective therapy for disorders that cause sleepiness.
- For correct interpretation, the MSLT must be performed following an all-night PSG.
- The MSLT consists of 5 nap opportunities to determine both severity of sleepiness and presence of 2 or more sleep onset REM periods for the diagnosis of narcolepsy. A shorter 4-nap test may be performed for determination of excessive sleepiness, but this test is not reliable for the diagnosis of narcolepsy unless at least 2 sleep onset REM periods (SOREMPs) have occurred.
- The absence of sleep on any nap opportunity is recorded as a sleep latency of 20 minutes.
- Mean sleep latency times (min) are interpreted as follows:
  - 0 to 5: severe sleepiness
  - 5 to 10: moderate sleepiness
  - 10 to 15: mild sleepiness

Appendix C. Maintenance of Wakefulness Test (MWT) (*Freedman 2019*)

- The MWT objectively measures the ability of an individual to remain awake for a defined period of time. It is based on the premise that individuals with a greater degree of sleepiness are less likely to remain awake than individuals with less sleepiness.
- The MWT is primarily used in a research setting to assess an intervention's ability to improve alertness. Some commercial driving companies utilize the MWT to assess a driver's ability to operate a vehicle safely, although the utility of the MWT in clinical practice is limited by the test's inability to accurately predict safety in real world settings.
- MWT Protocol:
  - The MWT should be performed following a standard protocol. Using a protocol minimizes the variables that can impact sleep latency, the test's primary measure. Several acceptable protocols exist including the following, which was endorsed by a task force from the AASM:
    - Patients should maintain their normal routine prior to the test. Upon arrival, they should be questioned to determine whether their sleep prior to the test was adequate in quality and quantity, and whether they feel alert. The MWT should be delayed if the patient reports suboptimal sleep or not feeling alert. A PSG on the prior night is not necessary. Urine drug testing may be indicated to ensure that the result is not influenced by substances other than prescribed medications and is usually performed on the morning of the MWT or as directed by the sleep clinician.
    - The MWT begins 1.5 to 3 hours after the patient's usual wake-up time. The patient is placed in a room with little or no external light. The only light source should be dim, slightly behind the patient's head, and just out of the patient's field of vision. The room temperature is based on the patient's comfort level. The patient sits upright in bed, with their back and head supported, and is instructed to try to stay awake as long as possible. Monitoring includes electroencephalography (EEG), electrooculography, mental or submental electromyography, and electrocardiography.
    - A session is ended after unequivocal sleep, or after 40 minutes if sleep does not occur. Sleep is considered unequivocal after 3 consecutive epochs of stage 1 sleep or 1 epoch of any other stage of sleep. For each session, the sleep latency is recorded. It is documented as being 40 minutes if the patient does not fall asleep.
    - This is repeated every 2 hours, until the patient has completed 4 sessions.
- Interpretation of MWT:
  - The primary measure from the MWT is the mean sleep latency. There are few data regarding what constitutes a normal mean sleep latency, as measured by the MWT. Among healthy individuals who complete the 4 session, 40-minute protocol described above, the mean sleep latency is approximately 30 minutes, with > 97% of individuals having a mean sleep latency ≥ 8 minutes. As a result, a mean sleep latency < 8 minutes is generally considered abnormal. Staying awake for at least 40 minutes during all 4 sessions is strong objective evidence that an individual can stay awake. A mean sleep latency between 8 and 40 minutes has uncertain significance.

Appendix D. Epworth Sleepiness Scale (ESS) (*Johns 1991*)

- The ESS is a self-administered questionnaire that provides a measurement of an individual's general level of daytime sleepiness.
- Patients are asked to rate on a scale of 0 to 3 how likely they would be to doze off or fall asleep in 8 situations that involve low levels of stimulation, relative immobility, and relaxation based on their usual way of life in recent times. The following question is rated for each situation using a scale of 0 to 3 as defined below:

- How likely are you to doze off or fall asleep in the following situations, in contrast to feeling just tired? This refers to your usual way of life in recent times. Even if you have not done some of these things recently, try to work out how they would have affected you. Use the following scale to choose the most appropriate number for each situation:
  - 0 = would never doze
  - 1 = slight chance of dozing
  - 2 = moderate chance of dozing
  - 3 = high chance of dozing
- The 8 situations include:
  - Sitting and reading
  - Watching TV
  - Sitting, inactive in a public place (eg, a theater or a meeting)
  - As a passenger in a car for an hour without a break
  - Lying down to rest in the afternoon when circumstances permit
  - Sitting and talking to someone
  - Sitting quietly after a lunch without alcohol
  - *In a car, while stopped for a few minutes in the traffic*
- Interpretation of ESS scoring (range, 1 to 24):
  - 1 to 6 points: normal sleep
  - 7 to 8 points: average sleepiness
  - 9 to 24 points: abnormal (possibly pathologic) sleepiness

Appendix E. Karolinska Sleepiness Scale (KSS) (*Akerstedt & Gillberg 1990*)

- The KSS is a 9-point Likert scale often used when conducting studies involving self-reported, subjective assessment of an individual's level of drowsiness at the time. The KSS scores are defined as follows:
  - 1 = extremely alert
  - 3 = alert
  - 5 = neither alert nor sleepy
  - 7 = sleepy, no difficulty remaining awake
  - 9 = extremely sleepy, fighting sleep
    - The steps in between have a scale value but no verbal label.

Appendix F. Stanford Sleepiness Scale (SSS) (*upenn.edu Web site*)

- The SSS is a subjective measure of sleepiness, frequently used for both research and clinical purposes. Whereas an instrument like the ESS examines general experiences of sleepiness over the course of an entire day, the SSS evaluates sleepiness at specific moments in time. Consisting of only 1 item, the scale requires respondents to select 1 of 7 statements best representing their level of perceived sleepiness. As a single-item measure, the scale is best suited for repeated use over the course of a research study or treatment intervention. The rating scale is as follows:
  - 1 = feeling active, vital, alert, or wide awake
  - 2 = functioning at high levels, but not at peak; able to concentrate
  - 3 = awake, but relaxed; responsive but not fully alert
  - 4 = somewhat foggy, let down
  - 5 = sleepy, woozy, fighting sleep; prefer to lie down
  - 6 = no longer fighting sleep, sleep onset soon; having dream-like thoughts
  - 7 = asleep

Appendix G. Sustained Attention to Response Task (SART) (*Fronczek et al 2006*)

- A number from 1 to 9 is shown to the patient 225 times in white on a black computer screen over a 4.3-minute period in a quiet room with dimmed lights. Each of the 9 numbers is shown 25 times in random order. The font size is chosen at random from 26, 28, 36, or 72 points. The numbers are presented in a predetermined and quasirandom way so that identical numbers were not clustered. Each number is presented for 250 milliseconds, followed by a blank screen for 900 milliseconds. Patients have to respond to the appearance of each number by pressing a small button, except when the number is a 3. Patients have to press the button before the next number appears and are instructed that accuracy is more important than speed. A complete SART takes 4 minutes and 20 seconds to perform. The SART error score consists of the total number of errors, expressed as the sum of the times a key was pressed when a 3 was presented, and the times when no key was pressed when it should have been.

Appendix H. AASM grading of evidence (*Morgenthaler et al 2007a*)

Classification of evidence

Evidence levels	Study design

I	Randomized, well-designed trials with low alpha and beta error,* or meta-analyses of RCTs with homogeneity of results
II	Randomized trials with high alpha and beta error, methodologic problems, or high-quality cohort studies*
III	Nonrandomized concurrently controlled studies (case-control studies)
IV	Case-control or cohort studies with methodological problems, or case series
V	Expert opinion, or studies based on physiology or bench research

*Alpha (type I error) refers to the probability that the null hypothesis is rejected when in fact it is true (generally acceptable at 5% or less, or $p < 0.05$). Beta (Type II error) refers to the probability that the null hypothesis is mistakenly accepted when in fact it is false (generally, trials accept a beta error of 0.20). The estimation of Type II error is generally the result of a power analysis. The power analysis takes into account the variability and the effect size to determine if sample size is adequate to find a difference in means when it is present (power generally acceptable at 80 to 90%).

Levels of recommendation

Term	Definition
Standard	This is a generally accepted patient-care strategy that reflects a high degree of clinical certainty. The term standard generally implies the use of level 1 evidence, which directly addresses the clinical issue, or overwhelming level 2 evidence.
Guideline	This is a patient-care strategy that reflects a moderate degree of clinical certainty. The term guideline implies the use of level 2 evidence or a consensus of level 3 evidence.
Option	This is a patient-care strategy that reflects uncertain clinical use. The term option implies either inconclusive or conflicting evidence or conflicting expert opinion.

Appendix I. EAN grading of evidence (*Brainin et al 2004*)

Evidence classification scheme for a therapeutic intervention

Evidence levels	Definition
Class I	An adequately powered prospective, randomized, controlled clinical trial with masked outcome assessment in a representative population or an adequately powered systematic review of prospective randomized controlled clinical trials with masked outcome assessment in representative populations. The following are required: (a) randomization concealment (b) primary outcome(s) is/are clearly defined (c) exclusion/inclusion criteria are clearly defined (d) adequate accounting for dropouts and crossovers with numbers sufficiently low to have minimal potential for bias (e) relevant baseline characteristics are presented and substantially equivalent among treatment groups or there is appropriate statistical adjustment for differences
Class II	Prospective matched-group cohort study in a representative population with masked outcome assessment that meets a through e above or an RCT in a representative population that lacks 1 criteria (a) through (e)
Class III	All other controlled trials (including well-defined natural history controls or patients serving as own controls) in a representative population, where outcome assessment is independent of patient treatment
Class IV	Evidence from uncontrolled studies, case series, case reports, or expert opinion

Evidence classification scheme for a diagnostic measure

Evidence levels	Definition
Level A	Established as effective, ineffective, or harmful) requires at least 1 convincing class I study or at least 2 consistent, convincing class II studies
Level B	Probably effective, ineffective, or harmful) requires at least 1 convincing class II study or overwhelming class III evidence
Level C	Possibly effective, ineffective, or harmful) rating requires at least 2 convincing class III studies

Appendix J. Micromedex recommendation, efficacy, and evidence ratings (*Micromedex Web site 2019*)

Strength of recommendation

Class I	Recommended	The given test or treatment has been proven to be useful, and should be performed or administered
Class IIa	Recommended in most cases	The given test, or treatment is generally considered to be useful, and is indicated in most cases.
Class IIb	Recommended in some cases	The given test, or treatment may be useful, and is indicated in some, but not most, cases.
Class III	Not recommended	The given test, or treatment is not useful, and should be avoided.
Class indeterminate	Evidence inconclusive	

Strength of evidence	
Category A	Category A evidence is based on data derived from: Meta-analyses of RCTs with homogeneity with regard to the directions and degrees of results between individual studies. Multiple, well-done randomized clinical trials involving large numbers of patients.
Category B	Category B evidence is based on data derived from: Meta-analyses of RCTs with conflicting conclusions with regard to the directions and degrees of results between individual studies. RCTs that involved small numbers of patients or had significant methodological flaws (eg, bias, drop-out rate, flawed analysis, etc.). Nonrandomized studies (eg, cohort studies, case-control studies, observational studies).
Category C	Category C evidence is based on data derived from: Expert opinion or consensus, case reports or case series.
No evidence	

Efficacy		
Class I	Effective	Evidence and/or expert opinion suggests that a given drug treatment for a specific indication is effective.
Class IIa	Evidence favors efficacy	Evidence and/or expert opinion is conflicting as to whether a given drug treatment for a specific indication is effective, but the weight of evidence and/or expert opinion favors efficacy.
Class IIb	Evidence is inconclusive	Evidence and/or expert opinion is conflicting as to whether a given drug treatment for a specific indication is effective, but the weight of evidence and/or expert opinion argues against efficacy.
Class III	Ineffective	Evidence and/or expert opinion suggests that a given drug treatment for a specific indication is ineffective.

REFERENCES

- Akerstedt T, Gillberg M. Subjective and objective sleepiness in the active individual. *Int J Neurosci*. 1990;52:29-37.
- Alshaikh MK, Tricco AC, Tashkandi M, Mamdani M, Straus SE, BaHammam AS. Sodium oxybate for narcolepsy with cataplexy: systematic review and meta-analysis. *J Clin Sleep Med*. 2012;8(4):451-458.
- American Heart Association (AHA). Why should I limit sodium? 2017. https://www.heart.org/-/media/dataimport/downloadables/8/2/0/pe-abh-why-should-i-limit-sodiumucm_300625.pdf?la=en&hash=FC0B16B18A81B3CC8371FAA4CC48D526471DC2CD. Accessed October 5, 2020.
- American Sleep Association Web site. https://www.sleepassociation.org/sleep-treatments/multiple-sleep-latency-test/. Accessed September 25, 2020.
- Bhattarai J, Sumerall S. Current and future treatment options for narcolepsy: a review. *Sleep Sci*. 2017;10(1):19-27.
- Billiard M, Dauvilliers Y, Dolenc-Grošelj L, Lammers GJ, Mayer G, Sonka K. Chapter 38. Section 6. Sleep Disorders. Management of narcolepsy in adults. European Academy of Neurology. 2011.
- Black J, Houghton WC. Sodium oxybate improves excessive daytime sleepiness in narcolepsy. *Sleep*. 2006;29(7):939-946.
- Black JE, Hull SG, Tiller J, Yang R, Harsh JR. The long-term tolerability and efficacy of armodafinil in patients with excessive sleepiness associated with treated obstructive sleep apnea, shift work disorder, or narcolepsy: an open-label extension study. *J Clin Sleep Med*. 2010;6(5):458-466.
- Brainin M, Barnes M, Baron JC, Gilhus NE, Hughes R, Selmaj K, Waldemar G; Guideline Standards Subcommittee of the EFNS Scientific Committee. Guidance for the preparation of neurological management guidelines by EFNS scientific task forces-revised recommendations 2004. *Eur J Neurol*. 2004(9):577-581.
- Carter LP, Henningfield JE, Wang YG, et al. A randomized, double-blind, placebo-controlled, crossover study to evaluate the human abuse liability of solriamfetol, a selective dopamine and norepinephrine reuptake inhibitor. *J Psychopharmacol*. 2018;32(12):1351-1361.
- Cheng P, Drake CL. Sleep-wake disturbances in shift workers. UpToDate Web site. Updated August 7, 2020. www.uptodate.com. Accessed September 27, 2020.
- Clinicaltrials.gov Web site. https://www.clinicaltrials.gov. Accessed September 27, 2020.
- Czeisler CA, Walsh JK, Roth T, et al. Modafinil for excessive sleepiness associated with shift-work sleep disorder. *N Engl J Med*. 2005;353:476-486.
- Czeisler CA, Walsh JK, Wesnes KA, Arora S, Roth T. Armodafinil for treatment of excessive sleepiness associated with shift work disorder: a randomized controlled study. *Mayo Clin Proc*. 2009;84:958-972.
- Dauvilliers Y, Bassetti C, Lammers GJ, et al; HARMONY I study group. Pitolisant versus placebo or modafinil in patients with narcolepsy: a double-blind, randomized trial. *Lancet Neurol*. 2013;12(11):1068-1075.

- Dauvilliers Y, Arnulf I, Szakacs Z, et al. Long-term use of pitolisant to treat patients with narcolepsy: Harmony III Study. *Sleep*. 2019;42(11):1-11.
- Eichler AF, Finlay G, Hoppin AG. What's new in sleep medicine. UpToDate Web site. Updated September 24, 2020. www.uptodate.com. Accessed September 24, 2020.
- FDA/CDER resources page. Food and Drug Administration Web site. http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm. Accessed September 25, 2020.
- Freedman N. Quantifying sleepiness. UpToDate Web site. Updated August 11, 2020. www.uptodate.com. Accessed September 27, 2020.
- Fronczek R, Middelkoop HA, van Dijk JG, Lammers GJ. Focusing on vigilance instead of sleepiness in the assessment of narcolepsy: high sensitivity of the Sustained Attention to Response Task (SART). *Sleep.* 2006; 29: 187-191.
- Golicki D, Bala MM, Niewada M, Wierzbicka A. Modafinil for narcolepsy: systematic review and meta-analysis. *Med Sci Monit*. 2010;16(8):177-186.
- Harsh JR, Hayduk R, Rosenberg R, et al. The efficacy and safety of armodafinil as treatment for adults with excessive sleepiness associated with narcolepsy. *Curr Med Res Opin*. 2006;22(4):761-774.
- Herdman M, Gudex C, Lloyd A. Development and preliminary testing of the new five-level version of EQ-5D (EQ-5D-5L). *Qual Life Res*. 2011;20:1727-1736.
- Johns MW. A new method for measuring daytime sleepiness: the Epworth sleepiness scale. *Sleep*. 1991;14(6):540-545.
- Kline LR. Clinical presentation and diagnosis of obstructive sleep apnea in adults. UpToDate Web site. Updated August 9, 2019. www.uptodate.com. Accessed September 25, 2019.
- Kryger MH. Management of obstructive sleep apnea in adults. UpToDate Web site. Updated April 1, 2020. www.uptodate.com. Accessed September 27, 2020.
- Kuan YC, Wu D, Huang KW, et al. Effects of modafinil and armodafinil in patients with obstructive sleep apnea: a meta-analysis of randomized controlled trials. *Clin Ther*. 2016;38(4):874-888.
- Lehert P, Falissard B. Multiple treatment comparison in narcolepsy: a network meta-analysis. *Sleep*. 2018;41(12):1-13..
- Malhotra A, Shapiro C, Pepin J, et al. Long-term study of the safety and maintenance of efficacy of solriamfetol (JZP-110) in the treatment of excessive sleepiness in participants with narcolepsy or obstructive sleep apnea. *Sleep*. 2020;43(2): 1-11.
- Mendoza TR, Wang XS, Cleeland CS, et al. The rapid assessment of fatigue severity in cancer patients: use of the Brief Fatigue Inventory. *Cancer*. 1999;85(5):1186-1196.
- Micromedex Web site 2020. https://www-micromedexsolutions-com. Accessed September 27, 2020.
- Mitler MM, Harsh J, Hirshkowitz M, Guilleminault C. Long-term efficacy and safety of modafinil (PROVIGIL(R)) for the treatment of excessive daytime sleepiness associated with narcolepsy. *Sleep Med.* 2000;1(3):231-243.
- Morgenthaler TI, Kapur VK, Brown TM, et al. Practice parameters for the treatment of narcolepsy and other hypersomnias of central origin. *Sleep*. 2007a; 30(12):1705-1711.
- Morgenthaler TI, Kapen S, Lee-Chiong T, et al. Practice parameters for the medical therapy of obstructive sleep apnea. *Sleep*. 2006;29(8):1031-1035.
- Morgenthaler TI, Lee-Chiong T, Alessi C, et al. Practice parameters for the clinical evaluation and treatment of circadian rhythm sleep disorders. An American Academy of Sleep Medicine report. *Sleep*. 2007b; 30(11):1445-1459.
- Nuvigil [package insert], North Wales, PA: Teva Pharmaceuticals USA, Inc.; March 2020.
- Pepin JL. Evaluation and management of residual sleepiness in obstructive sleep apnea. UpToDate Web site. Updated July 14, 2020. www.uptodate.com. Accessed September 27, 2020.
- Plazzi G, Ruoff C, Lecendreux M, et al. Treatment of paediatric narcolepsy with sodium oxybate: a double-blind, placebo-controlled, randomised-withdrawal multicentre study and open-label investigation. *Lancet Child Adolesc Health*. 2018; 2:483-894.
- Provigil [package insert], North Wales, PA: Teva Pharmaceuticals USA, Inc.; March 2020.
- Scammell TE. Clinical features and diagnosis of narcolepsy in adults. UpToDate Web site. Updated August 11, 2020a. www.uptodate.com. Accessed September 27, 2020.
- Scammell TE. Treatment of narcolepsy in adults. UpToDate Web site. Updated September 22, 2020b. www.uptodate.com. Accessed September 25, 2020.
- Schweitzer PK, Rosenberg R, Zammit GK, et al. Solriamfetol for excessive sleepiness in obstructive sleep apnea (TONES 3): A randomized controlled trial. *Am J Respir Crit Care Med*. 2019;199(11):1421-1431.
- Stanford Sleepiness Scale. Web site. https://www.med.upenn.edu/cbti/assets/user-content/documents/Stanford%20Sleepiness%20Scale.pdf. Accessed October 14, 2020.
- Strollo PJ, Hedner J, Collop N, et al. Solriamfetol for the treatment of excessive sleepiness in OSA. A placebo-controlled randomized withdrawal study. *Chest*. 2019;155(2): 364-374.
- Sunosi [dossier], Palo Alto, CA: Jazz Pharmaceuticals, Inc.; April 2019.
- Sunosi FDA summary review. FDA Web site. March 20, 2019. https://www.accessdata.fda.gov/drugsatfda_docs/nda/2019/211230Orig1Orig2s000SumR.pdf. Accessed October 25, 2020.
- Sunosi [package insert], Palo Alto, CA: Jazz Pharmaceuticals, Inc.; October 2019.
- Sunosi press release. March 20, 2019. https://investor.jazzpharma.com/news-releases/news-release-details/jazz-pharmaceuticals-announces-us-fda-approval-sunositm. Accessed October 14, 2020.
- SUNOSI™ - Long-Term Safety and Maintenance of Efficacy. SUN_CRL004_Long-Term Safety and Maintenance of Efficacy_v01_04.03.19. Jazz Pharmaceuticals Medical Information response letter. Received April 16, 2019.
- Szabo ST, Thorpy MJ, Mayer G, Peever JH, Kilduff TS. Neurobiological and immunogenetic aspects of narcolepsy: Implications for pharmacotherapy. *Sleep Med Rev*. 2019;43:23-36.
- Szakacs Z, Dauvilliers Y, Mikhaylov V, et al; HARMONY-CTP study group. Safety and efficacy of pitolisant on cataplexy in patients with narcolepsy: a randomised, double-blind, placebo-controlled trial. *Lancet Neurol*. 2017;16(3):200-207.
- Thorpy MJ, Shapiro C, Mayer G, et al. A randomized study of solriamfetol for excessive sleepiness in narcolepsy. *Ann Neurol*. 2019; 85:359-370.
- Thorpy MJ, The clinical use of the multiple sleep latency test. The Standards of Practice Committee of the American Sleep Disorders Association. *Sleep*. 1992;15(3):268-276.
- U.S. Xyrem Multicenter Study Group. Sodium oxybate demonstrates long-term efficacy for the treatment of cataplexy in patients with narcolepsy. *Sleep Med*. 2004;5(2):119-123.
- Wakix [package insert], Plymouth Meeting, PA: Harmony Biosciences LLC; October 2020.
- Wakix FDA summary review. FDA Web site. August 14, 2019. https://www.accessdata.fda.gov/drugsatfda_docs/nda/2019/211150Orig1s000SumR.pdf. Accessed September 25, 2020.

- Wakix FDA clinical review. FDA Web site. August 14, 2019. https://www.accessdata.fda.gov/drugsatfda_docs/nda/2019/211150Orig1s000MedR.pdf. Accessed September 27, 2020.
- Wakix [dossier], Plymouth Meeting, PA: Harmony Biosciences LLC; September 2019.
- Xyrem [package insert], Palo Alto, CA: Jazz Pharmaceuticals, Inc.; July 2020.
- Xywav [package insert], Palo Alto, CA: Jazz Pharmaceuticals, Inc.; July 2020.
- Xywav [dossier], Palo Alto, CA: Jazz Pharmaceuticals, Inc.; August 2020.

Monograph created by: J. D'Aloia, Pharm.D.
Reviewed by: Amy Schwalm, Pharm.D.

Publication date: 12/2/2020