



1-1-2022

pitolisant, a novel histamine-3 receptor competitive antagonist, and inverse agonist, in the treatment of excessive daytime sleepiness in adult patients with narcolepsy

Noeen Sarfraz
Louisiana State University Health Science Center

David Okuampa
Louisiana State University

Hannah Hansen
Louisiana State University

Mark R. Alvarez
Louisiana State University

Elyse M. Cornett
Louisiana State University

See next page for additional authors.
Follow this and additional works at: <https://scholarlycommons.pacific.edu/phs-facarticles>



Part of the [Medicine and Health Sciences Commons](#)

Recommended Citation

Sarfraz, N., Okuampa, D., Hansen, H., Alvarez, M. R., Cornett, E. M., Kakazu, J., Kaye, A. M., & Kaye, A. D. (2022). pitolisant, a novel histamine-3 receptor competitive antagonist, and inverse agonist, in the treatment of excessive daytime sleepiness in adult patients with narcolepsy. *Health Psychology Research*, 10(3), 34222. DOI: [10.52965/001c.34222](https://doi.org/10.52965/001c.34222)
<https://scholarlycommons.pacific.edu/phs-facarticles/611>

This Article is brought to you for free and open access by the Thomas J. Long School of Pharmacy at Scholarly Commons. It has been accepted for inclusion in School of Pharmacy Faculty Articles by an authorized administrator of Scholarly Commons. For more information, please contact mgibney@pacific.edu.

Authors

Noeen Sarfraz, David Okuampa, Hannah Hansen, Mark R. Alvarez, Elyse M. Cornett, Juyeon Kakazu, Adam M. Kaye, and Alan David Kaye

General

pitolisant, a novel histamine-3 receptor competitive antagonist, and inverse agonist, in the treatment of excessive daytime sleepiness in adult patients with narcolepsy

Noeen Sarfranz, MD, MPH¹, David Okuampa², Hannah Hansen², Mark Alvarez², Elyse M. Cornett, PhD³, Juyeon Kakazu, BS, MS⁴, Adam M. Kaye, PharmD⁵, Alan D. Kaye, MD, PhD³

¹ Department of Psychiatry, Louisiana State University Health Shreveport, ² College of Medicine, Louisiana State University Health Shreveport, ³ Department of Anesthesiology, Louisiana State University Health Shreveport, ⁴ Georgetown University School of Medicine, ⁵ Department of Pharmacy Practice, Thomas J. Long School of Pharmacy and Health Sciences, University of the Pacific

Keywords: Pitolisant, excessive daytime sleepiness, narcolepsy, NT1, NT2

<https://doi.org/10.52965/001c.34222>

Health Psychology Research

Vol. 10, Issue 3, 2022

Narcolepsy is a debilitating sleep disorder that presents with excessive daytime sleepiness (EDS) and cataplexy, which is a sudden paralysis of muscle tone triggered by strong emotions such as laughing. It is also associated with many other disorders, including psychiatric disorders, neurologic illnesses, and medication side effects. Common causes of delayed and incorrect diagnoses of these conditions include lack of physician familiarity with narcolepsy symptoms and comorbidities which mask narcolepsy signs and symptoms. Current pharmacologic therapies include Modafinil and Armodafinil for EDS and sodium oxybate for cataplexy. This review discusses the epidemiology, pathophysiology, risk factors, presentation, treatment of narcolepsy, and the role of a novel drug, Pitolisant, in the treatment of EDS in adults with narcolepsy. Pitolisant is a histamine-3 receptor (H3R), competitive antagonist, and inverse agonist, acting through the histamine system to regulate wakefulness. It is a novel drug approved in August 2019 by the FDA, is not classified as a controlled substance, and is approved for use in Europe and the United States to treat EDS and cataplexy in narcolepsy. Recent phase II and III trials have shown that Pitolisant helps reduce the ESS score and cataplexy. In summary, based on comparative studies, recent evidence has shown that Pitolisant is non-inferior to Modafinil in the treatment of EDS but superior to Modafinil in reducing cataplexy.

INTRODUCTION

Narcolepsy is a disabling neurological disorder characterized by excessive daytime sleepiness (EDS) and disturbed nighttime sleep.¹ It is estimated that 1 in every 2000 individuals is affected by narcolepsy, and about half are undiagnosed.¹ The onset of narcolepsy is in adolescence or early adulthood; however, diagnosis is usually delayed by 8-12 years.² Common causes of delayed and incorrect diagnoses include lack of physician familiarity with narcolepsy symptoms and comorbidities that mask narcolepsy symptoms.^{1,3} The International Classification of Sleep Disorder (ICSD) has categorized narcolepsy into two subtypes: Narcolepsy Type 1 (NT1) and Narcolepsy Type 2 (NT2).² NT1 is caused

by an extensive loss of hypothalamic neurons that produce hypocretin 1 and 2, which are neuropeptides responsible for regulating sleepiness and wakefulness.^{2,4} NT1 and NT2 share a clinical profile; however, patients with NT1 classically present with cataplexy, sudden paralysis of muscle tone triggered by strong emotions such as laughing.^{1,2} EDS is defined as unintentional sleepiness, or the inability to maintain desired wakefulness, which affects one's functional ability.⁵ A common cause of EDS is insufficient sleep; however, EDS is also a symptom and manifestation of medical disorders (narcolepsy, obstructive sleep apnea (OSA), restless leg syndrome, major depressive disorder, stroke, Parkinson's disease, traumatic brain injury, neurologic lesion, and bipolar disorder).⁵ Prescription and over-the-counter medications that can cause EDS includes beta-

^a Corresponding author:

Juyeon Kakazu, BS, MS
Georgetown University School of Medicine
3900 Reservoir Road NW
Washington, D.C., 20007
Phone: (808) 351-2379
jck107@georgetown.edu

blockers, sedative/hypnotics, anticonvulsants, and opioids.⁵ Lack of sleep and/or inability to maintain wakefulness leads to reduced quality of life and a potentially unsafe working environment with public safety risks.⁵ Treatment of narcolepsy involves pharmacologic and non-pharmacologic interventions, with the primary aim of increasing wakefulness and reducing cataplexy attacks.⁶ Non-pharmacologic interventions include scheduled napping, proper sleep hygiene, and avoidance of drugs that induce daytime sleepiness.⁶ Wake-promoting agents, such as Modafinil and Armodafinil, are first-line pharmacotherapies for EDS in narcolepsy.⁶ The exact mechanism of action in promoting wakefulness is elusive, but there appears to be an increase in dopaminergic signaling via blocking dopamine reuptake.⁶ Solriamfetol, norepinephrine, and dopamine reuptake inhibitor are indicated to improve wakefulness in EDS among individuals with narcolepsy or OSA.⁷

Pitolisant is a novel noncontrolled drug approved by the Food and Drug Administration (FDA) in August 2019 to treat EDS in adults with narcolepsy. Pitolisant is a histamine-3 receptor (H3R), competitive antagonist, and inverse agonist, acting through the histamine system to regulate wakefulness.^{6,7} This review will discuss the epidemiology, pathophysiology, risk factors, presentation, and treatment of narcolepsy. Further, we will discuss drug information, mechanism of action, pharmacokinetics, and pharmacodynamics of Pitolisant. Finally, we will compare several Pitolisant clinical trials to determine safety and efficacy.

METHODS

We conducted literature searches using PubMed and Google Scholar between (insert date here). Articles were chosen based on relevance to pitolisant and its therapeutic effects on narcolepsy. We selected primary literature as well as clinical trial studies to reflect the validity of the review. Older articles were included as well to refer to previous background information.

The PubMed and Google Scholar keywords searched were as follows: pitolisant, narcolepsy, excessive daytime sleepiness, NT1, NT2, and histamine-3 receptor.

EPIDEMIOLOGY

Given the delay in diagnosing and masking symptoms with comorbidities, the prevalence and incidence of narcolepsy across ages, ethnicities, and genders have been difficult to estimate. A recent cross-sectional study in the United States between 2008-2010 shows that the prevalence of narcolepsy was disproportional within age and gender.⁸ According to this study, the overall prevalence of narcolepsy is 79.4/100,000 persons, with females having a greater prevalence (91.8/100,000 persons) compared to males (65.8/100,000 persons).⁹ Ages 21-30 have the highest prevalence (128.5/100,000), and females within this category have a higher prevalence than males.⁹ Patients with narcolepsy have a high burden of psychiatric comorbidities, with the greatest prevalence in anxiety and mood disorders in younger age groups.³ A recent retrospective study, 2008-2010, shows a 1.5 fold excess mortality in narcoleptic

patients vs. a non-narcoleptic population.¹⁰ Mortality rates in 2008 (1.14%), 2009 (1.17%) and 2010 (1.16%) were substantially higher compared to the non-narcoleptic population: 2008 (0.78%), 2009 (0.77%), and 2010 (0.79%).¹⁰ In the narcoleptic population, the highest mortality rates were observed among younger age groups, and the lowest mortality rates were among the older age group.¹⁰

RISK FACTORS

Risk factors for narcolepsy include age, genetics, family history, environmental risk, and psychiatric comorbidities.¹¹ Genetic factors, such as human leukocyte antigen (HLA), play a role in developing NT1.² The HLA-DQB1*06:02 allele is the main genetic risk factor in 86-98% of NT1 patients.² HLA-DQB1*06:02 positivity is higher in African Americans (91%) vs. other groups (Caucasian, 76%, Asian, 80%, Latino, 65%), which positively correlates with an earlier age of onset of narcolepsy.¹² The H1N1 influenza pandemic between 2009 and 2010 resulted in a spike of narcolepsy among children and teenagers in Scandinavia, Europe, and China.^{2,4} This surge, particularly in Europe and Scandinavia, was linked to a vaccine against H1N1 (Pandemrix), which affected children and teenagers with the HLA-DQB1*06:02 gene.^{2,4} This suggests that the combination of the HLA-DQB1*06:02 allele, young age, and particular immune stimuli increase the risk of narcolepsy.⁴ Most cases of narcolepsy are sporadic; however, first-degree relatives are at higher risk of developing narcolepsy than the general population.²

PATHOPHYSIOLOGY

Recent studies regarding the pathophysiology of narcolepsy mostly focus on the selective neuronal loss of orexin-A and orexin B, synonymously, hypocretin 1, and hypocretin 2, respectively.¹³ Orexins are small neuropeptides produced solely in the lateral hypothalamus, stabilizing sleep-wakefulness and regulating rapid eye movement (REM) sleep.^{13,14} The mechanism by which orexin levels decrease is not understood, but emerging evidence suggests an autoimmune process.¹³ Selective loss of orexin neurons is a distinctive phenotype widely associated with narcolepsy with cataplexy (NT1) due to a decrease in cerebrospinal fluid (CSF) orexin level compared to NT2 with normal CSF orexin level.¹³ Neurologically, orexin-A and orexin-B have an excitatory effect on postsynaptic neurons via the orexin-1 receptor (OX1R) and orexin-2 receptor (OX2R). This excites wake-promoting neurons in the basal forebrain (BF), tuberomammillary nucleus (TMN), pedunculo pontine, and laterodorsal tegmental nuclei (PPT-LDT), dorsal raphe (DR), and locus coeruleus (LC).¹³ Orexin neurons also prevent muscle paralysis during the wakeful period by activating ventrolateral periaqueductal grey and lateral pontine tegmentum (vlPAG-LPT), DR, and LC, which inhibit the sublateral nucleus (SLD).^{13,14} SLD drives muscle paralysis during REM sleep by inhibiting motor neurons through GABAergic premotor neurons.¹³ In narcolepsy, the absence of orexin leads to the loss of the excitatory drive to activate wake-promoting neurons, coupled with decreased

SLD inhibition. These result in poor wakefulness maintenance, poor REM sleep regulation, and cataplexy.^{13,14}

PRESENTATION

The onset of narcolepsy is between the ages of 10-25 years old, though the manifestation of symptoms can begin at any age.¹⁵ EDS is the most common symptom. Though it is present in narcolepsy with and without cataplexy is also associated with many other disorders, including psychiatric disorders, neurologic illnesses, and medication side effects.¹⁶ Patients who present with EDS should also be evaluated for fatigue due to their overlapping presentations.¹⁶ One way to distinguish fatigue from EDS is by using the Multiple Sleep Latency Test (MSLT), which is used to measure sleepiness; patients with EDS will show short sleep latencies; MSLT results are normal in fatigue.¹⁶ The diagnostic criteria established by ICSID include chronic excessive sleepiness lasting more than three months, a mean sleep latency less than or equal to eight minutes, and two or more sleep-onset rapid-eye-movement periods (SOREMPs).⁷ Cataplexy is always associated with NT1, and it is pathognomonic of the disease.¹⁷ Patients present with varying degrees of muscle paralysis and weakness in arms, legs, and facial muscles, which can be triggered by strong emotions, such as laughter.¹⁸ Cataplexy attacks last between a few seconds to minutes, after which the patient may fall asleep.¹⁸ Reduction in hypocretin levels leads to a change in metabolism, which disrupts baseline energy homeostasis, causing obesity, type-II diabetes mellitus, lower body temperature, and lower blood pressure.¹⁸ Other symptoms associated with narcolepsy include sleep paralysis, sleep-related hallucinations, and sleep fragmentation.¹⁵

CURRENT TREATMENT OF NARCOLEPSY

There is no cure for narcolepsy; therefore, treatment is centered around improving daily functioning by decreasing EDS symptoms, nocturnal sleep disruption, cataplexy, hypnagogic/hypnopompic hallucinations, sleep paralysis, and associated comorbidities.^{1,3,5,8,18} Narcolepsy is typically treated with wake-promoting drugs and lifestyle changes.^{1,3} Patients with mild symptoms may be able to use solely nonpharmacologic methods. However, most will require medication.^{1,3} Lifestyle changes that may improve narcolepsy symptoms include improving sleep hygiene, creating a structured sleeping schedule, and taking one or two scheduled naps in the afternoon.^{1,3} 20-minute naps typically improve EDS, though some patients may require longer naps.^{1,3}

The sustained attention to response task (SART), Epworth sleepiness scale (ESS), and maintenance of wakefulness test (MWT) measure the treatment response to narcolepsy and are used to compare treatments.⁴ The global clinical impression of severity (CGI-S) is a six-point scale, rated using a clinical interview, measuring EDS and cataplexy severity. The CGI-S is used to calculate the global clinical impression of change (CGI-C), which measures disease improvement with treatment.⁴ Studies use these tools

to determine the effectiveness of new drugs, develop treatment guidelines, and monitor treatment progression.

Modafinil and armodafinil (the r-enantiomer of modafinil) are first-line therapies for EDS in narcolepsy.^{1,3,18} Modafinil promotes wakefulness but does not treat cataplexy and has low abuse potential.^{3,18} Modafinil works by increasing the extracellular concentration of dopamine in the hypothalamus' wake-generating sites by selectively and competitively binding the dopamine transporter.^{3,18} Some studies suggest that modafinil may be more effective as split dosing (either 200 mg in the morning and 200 mg in the afternoon or two doses of 600 mg) rather than a single dose in the morning.¹⁸ Armodafinil has a longer duration of action than modafinil, and a smaller dose (100-250 mg/day) is required to be effective.¹⁸ The mean monthly drug-specific pharmacy costs of armodafinil are lower compared to modafinil.¹⁸ Stimulants are indirect sympathomimetics and are second-line therapy for EDS. Methylphenidate and amphetamines, including dextroamphetamine, amphetamine-dextromethamphetamine combination, and amphetamine sulfate, promote wakefulness by increasing the release of dopamine, noradrenaline, and serotonin and inhibiting the dopamine transporter, which increases amine concentration in the synapse.¹⁸ Rebound hypersomnia, abuse, and tolerance are potential side effects of amphetamines, so they are only used under specific circumstances.¹⁸ An intermediate-release formulation of methylphenidate may be used if first-line therapy is unsuccessful.¹⁸

Patients who solely use amphetamines for EDS will most likely have better results and lower risk of recreational abuse by taking an extended-release formulation, such as MES-amphetamine (Adderall XR) or lisdexamfetamine dimesylate (Vyvanse).¹⁸ Additionally, patients who partially respond to modafinil or armodafinil and who also need to maintain wakefulness in the afternoon may need supplemental, short-acting stimulants, preferably methylphenidate.¹⁸ Additional side effects of amphetamines include cardiac risks, anorexia, insomnia, and appetite suppression.¹⁸

Solriamfetol (JZP-110), a dopamine and norepinephrine reuptake inhibitor, was recently approved to treat EDS in adults.⁵ Its efficacy was demonstrated via significant improvements on the MWT in randomized control trials.^{5,8} It has shown no clinical efficacy in treating cataplexy.^{5,8} Sodium oxybate, a metabolite of γ -amino butyric acid (GABA), is a first-line therapy for EDS and cataplexy, sleep paralysis, severe breathing problems, seizure, loss of consciousness, hypnagogic hallucinations or death.¹⁹ Thus, sale is restricted to certified pharmacies. At doses of six and nine grams, sleep attack frequency was significantly reduced. However, it takes at least eight weeks before the effectiveness of reducing sleepiness becomes apparent.¹⁸ Nine-gram doses also decrease nocturnal awakenings.¹⁸ Sodium oxybate, taken with Modafinil, shows the greatest improvement in EDS.¹⁸ Sodium oxybate side effects include confusion, anxiety, dizziness, and nausea.

Recent developments in narcolepsy treatment have been focused on non-hypocretin and hypocretin-based therapies and immunotherapy.¹⁸ Non-hypocretin therapies being developed include histamine receptor antagonists (such as

Pitolisant), novel monoaminergic reuptake inhibitors, GABA_B receptor agonists, GABA_A receptor modulators, slow-wave sleep enhancers, TRH and TRH analogs, and melanin-concentrating hormone receptor modulators.¹⁸ Hypocretin-based therapies include cell transplantation, stem cells, hypocretin peptide replacement, and gene replacement therapy.¹⁸ Cell transplantation, stem cells, and gene replacement therapy have only been studied in animal models.¹⁸ Hypocretin peptide replacement would theoretically work well in type 1 narcoleptic patients, whose disease is characterized by loss of hypocretin (orexin) neurons.^{5,18} However, this has not been successful since hypocretin peptides cannot cross the blood-brain barrier significantly to cause favorable effects.⁵ Finally, immunotherapy aims to reverse hypocretin neuronal cell destruction associated with narcolepsy type I.¹⁸ Studies using plasmapheresis, corticosteroids, and intravenous immunoglobulin infusions have shown variable results, and structured treatment guidelines have been limited by available research studies being too small and uncontrolled.¹⁸

Pitolisant (Wakix) is a first-in-class non controlled drug with a novel mechanism of action for narcolepsy treatment, which sets it apart from preexisting therapies.^{13,15} It is approved for treatment of narcolepsy type 1 and 2 and is recognized as an orphan drug by the EMA and US Food and Drug Administration.¹³ In Phase III trials, Pitolisant decreased the frequency of cataplexy attacks, reduced EDS, and improved the level of attention on sustained attention to response tasks.^{5,18} Pitolisant also significantly reduced hypnagogic hallucinations and sleep paralysis.⁵ Its non-inferiority to current treatment options has not been effectively demonstrated. Additional long-term RCTs comparing Pitolisant to modafinil and sodium oxybate are needed to elucidate its effectiveness in treatment and possible use as a possible first-line agent.¹³

DRUG INFORMATION

Pitolisant is taken orally.^{1,3,5} Internationally, tablet strengths are listed as 4.5 mg and 18 mg, whereas the US tablets are labeled as 4.45 mg and 17.8 mg.¹ The initial dose to treat narcolepsy, including EDS and cataplexy, is 8.9 mg once daily for one week, increased to 18.8 mg once daily the following week, and then increased to a maximum dose of 36.5 mg once daily in the third week, based on response.^{1,3} Doses can be reduced as need by 4.5 mg/day.³ If a dose is missed, the next dose may be administered the following morning.¹ No rebound effect was reported during clinical trials.⁴ The 4.45 mg oral tablets cost \$113.70 each.¹ The 17.8 mg tablets cost \$227.40 each.¹

Doses may need to be adjusted under certain conditions. For CYP2D6 poor metabolizers, the treatment is as above for the first week, but the maximum dose is 17.8 mg once daily instead of 36.5 mg once daily.^{1,5} Significant drug interactions exist with concomitant therapy, and a drug interaction database needs to be consulted before planning a dosing regimen.^{1,5} For renal impairment with eGFR 15 to <60 mL/minute/1.73 m², the initial dose is at 8.9 mg once daily for one week, but the maximum dose increase is 17.8 mg once daily. For eGFR < 15 mL/minute/1.73 m², Pitolisant is not recommended.¹ Pitolisant is contraindicated in in-

stances of severe hepatic impairment and in anyone who develops hypersensitivity to the drug or any component of the formulation.¹ Avoid use in patients with known QT prolongation or patients who take other agents known for QT prolongation (e.g. Methadone, Citalopram, Escitalopram, etc.).^{1,4} Avoid use in patients with cardiac arrhythmias or at increased risk of torsades de pointes.¹ The risk of adverse events is greater in those with hepatic or renal impairment.^{1,4} Renal and hepatic function baseline should be established and monitored as clinically indicated.¹ Drug interactions typically include substances that affect the concentration of CYP2D6 substrates.^{1,4} CYP2D6 inhibitors may increase the serum concentration of Pitolisant.¹ Pitolisant use with moderate CYP2D6 inhibitors needs to be monitored, while the dose of Pitolisant needs to be reduced by half with the use of strong CYP2D6 inhibitors.¹ Ajmaline, lumefantrine, and cobicistat may increase the serum concentration of CYP2D6.¹ Antihistamines, tricyclic antidepressants, and mirtazapine may lower the therapeutic effect of Pitolisant.¹ Pitolisant may decrease the serum concentration of hormonal contraceptives, and patients should be advised to use non-hormonal contraceptives while on Pitolisant.^{1,4} CYP3A4 inducers may decrease the serum concentration of Pitolisant.¹ Pitolisant dosing may need to be doubled over seven days if a new drug is started and known to be a strong CYP3A4 inducer.

Adverse reactions to Pitolisant in the HARMONY I trial included headache (35%), insomnia (10%), abdominal discomfort or pain (6%), and nausea (6%).^{1,2} One subject had a serious adverse event of abdominal discomfort related to Pitolisant.² In a retrospective chart review, the most common adverse events were epigastric and abdominal pain (15.4%), increased appetite (14.1%), weight gain (14.1%), headache (12.8%), insomnia (11.5%), and anxiety (9%).² Other studies have shown increased heart rate (3%), anxiety (5%), hallucinations (3%), irritability (3%), sleep disturbance (3%), cataplexy (2%), xerostomia (2%), decreased appetite (3%), musculoskeletal pain (5%), and upper respiratory tract infection (5%).¹ At very high doses (108-216 mg), a slight QTc interval prolongation has been observed.^{1,3,4} Migraine, abnormal behavior, abnormal dreams, sleep paralysis, sleep-talking, bipolar disorder, depressed mood, epilepsy, fatigue, anhedonia, pruritus, and suicidal ideation have also been observed, but with an unknown frequency.¹ Adverse event during pregnancy was noted in some animal studies, but further data collection monitoring Pitolisant's effects in pregnancy and infancy is ongoing.^{1,4} The presence of Pitolisant in breast milk is unknown.¹ No drug abuse potential was observed with Pitolisant.³

MECHANISM OF ACTION

Pitolisant is orally active and a potent, selective histamine H₃-receptor antagonist/inverse agonist.¹ H₃-receptors are primarily located in the cerebral cortex, hypothalamus hippocampus, and basal ganglia.³ Pitolisant's blockade of histamine auto-receptors increases histamine concentration and histaminergic activity in the brain.^{1,4} Histaminergic neurons have widespread projections throughout the brain that play a major role in arousal.^{1,2} Histaminergic neurons of the tuberomammillary nucleus of the hypothalamus are

particularly important in maintaining vigilance under certain environmental and behavioral conditions.² Increased histamine concentration in the hypothalamus is thought to contribute to Pitolisant's role in treating EDS and catalepsy.⁴ Pitolisant also modulates other neurotransmitters, increasing acetylcholine, noradrenaline, and dopamine release in the brain.^{1,3}

PHARMACOKINETICS/ PHARMACODYNAMICS

Pitolisant enhances the level and duration of wakefulness and alertness, according to the MWT and SART, both of which objectively measure the ability to sustain wakefulness.¹ Pitolisant is absorbed rapidly after oral administration, reaching peak plasma concentration approximately three hours after administration.^{1,3,4} Pitolisant has a plasma half-life of about 10-12 hours and reaches a steady-state in about five-six days.^{3,4} Pitolisant has approximately equal distribution between red blood cells and plasma and exhibits high serum protein-binding (>90%).^{1,3,4} Pitolisant is primarily eliminated in the urine (63%) through an inactive, non-conjugated metabolite (BP2.951) and a glycine-conjugated metabolite.^{3,4} Pitolisant is also excreted through expired air (25%) and in feces (<3%).⁴ CYP3A4 and CYP2D6 form the major non-conjugated metabolites of Pitolisant, including hydroxylated derivatives and cleaved forms found in serum and urine.^{1,3} The primary inactive metabolite formed by CYP3A4 and CYP2D6 is 5-aminovaleic acid.³ The major conjugated metabolites are two glycine conjugates of an acid metabolite and a glucuronide of a ketone metabolite.¹ In vitro studies of Pitolisant have suggested it to be a CYP3A4, CYP1A2, and CYP2B6 inducer, along with CYP2D6 and OCT1 inhibitors.^{3,4} In vitro studies have also suggested that Pitolisant is not a substrate or an inhibitor of human P-glycoprotein and breast cancer resistance protein.^{3,4} $AUC_{0-\infty}$ is increased by about 2.3 when Pitolisant dose is doubled from 27 to 54 mg.^{3,4} In patients 68 to 80 years old, Pitolisant's pharmacokinetics is similar to that in younger patients.^{3,4} Slight variation in pharmacokinetics is shown in patients over 80 years old, but it has no clinical relevance.⁴ AUC and C_{max} are typically increased by a factor of 2.5, without impacting the half-life, in patients with renal impairment (creatinine clearance between 15 to 89 mL/min).⁴ No significant changes were seen with mild hepatic impairment (Child-Pugh A). However, AUC increased by 2.4, and the half-life doubled in patients with moderate hepatic impairment (Child-Pugh B).⁴

CLINICAL STUDIES: SAFETY AND EFFICACY

PHASE II STUDIES

Three-phase II trials were undertaken to demonstrate the efficacy and safety of Pitolisant in narcoleptic patients. The P05-03 study was a single-blind, multicenter, placebo-controlled study, in which 22 narcoleptic patients were assigned a seven-day course of a placebo, followed by a daily regimen of 40 mg Pitolisant taken in the morning. In evaluating response to active treatment, participants saw a notable reduction in their Epworth Sleepiness Scale (ESS) scores from a baseline of 17.55±3.89 to 11.81±6.11. These

results represent a 4.86±5.12 reduction in ESS compared to placebo) and a 5.85±5.51 reduction relative to baseline. The P05-03 study noted no significant decrease in ESS relative to baseline ($p>0.05$).²⁰ The P06-06 study was run as a multicenter, open-label Phase II trial, wherein 26 participants were evaluated for response to an increasing dose of Pitolisant.²⁰ This escalating regimen involved participants receiving either 10, 20, or 40 mg daily dosages for a maximum of nine months. Participants were evaluated at one, three, and nine-month intervals, demonstrating a reduction in ESS of 4.8, 5.3, and 6.9 points, respectively.²⁰

INITIAL HARMONY TRIALS

Harmony I analyzed 110 narcoleptic patients from 32 treatment centers across Europe, 95 of which were randomly assigned to either Pitolisant ($n=32$), modafinil ($n=33$), or placebo ($n=30$) for eight weeks. The efficacy of Pitolisant was shown primarily via two double-blind, multicenter, parallel-group, placebo-controlled randomized trials, every eight weeks in duration with a flexible dosing schedule. In each study, researchers defined the measure of efficacy as a minimal clinically relevant difference in final ESS score between treatment and placebo groups of (3 points (20). Treatment schedule over eight weeks: three weeks of flexible dosing (10, 20, or 40 mg/day of Pitolisant; 100, 200, or 400 mg/day of Modafinil), followed by five weeks of a steady dose of the assigned therapy. By the end of eight weeks, mean ESS score reductions were -3.4±4.2 for the placebo group, -5.8±6.2 in the Pitolisant group, and -6.9±6.2 in the Modafinil group. Thus, Pitolisant demonstrated a significant improvement in outcome relative to placebo (a difference of -3.3 with a 95% CI of -5.83 to -0.83; $p=0.024$). This superiority was further demonstrated by differing measures of the Maintenance of Wakefulness Test (MWT) between the Pitolisant and placebo groups, demonstrating a difference of 1.47 (95% CI of 1.01 to -2.14; $p=0.044$). However, Harmony I did not demonstrate Pitolisant's superiority relative to modafinil, showing instead a mean ESS difference of only 0.12 (95% CI of -2.5 to 2.7; $p>0.250$) between these groups. Thus, the authors of Harmony I demonstrated the efficacy of Pitolisant (up to a 40 mg daily dose) relative to placebo, but not relative to standard Modafinil regimens.²⁰

Harmony Ibis was the second RCT to demonstrate Pitolisant's efficacy in treating narcolepsy.²⁰ It evaluated 165 participants, randomly dividing them into Pitolisant ($n=67$), Modafinil ($n=65$), or placebo ($n=33$) groups. This study used a flexible dosing model for the first three weeks of treatment: 10 or 20 mg daily of Pitolisant; or 100, 200, or 400 mg daily of Modafinil. This period of flexible dosing was followed by five weeks of stable dosing. Following the eight-week regimen, mean ESS score reductions were: 3.6±5.6 for placebo, -4.6±4.6 for Pitolisant, and -7.8±5.9 for Modafinil. Whereas Pitolisant demonstrated efficacy relative to baseline in Harmony I, Harmony Ibis noted a difference in mean ESS scores of only -1.94 (95% CI of -4.005 to -0.07; $p=0.06$) between Pitolisant and placebo treatments, thus failing to meet the criterion for efficacy of ≥ 3 points. Again, in evaluating the treatments' effect on ESS scores, non-inferiority of Pitolisant relative to Modafinil could not be established in this RCT either, as data demonstrate a difference of -2.75

(95% CI -4.48 to -1.02), which failed to meet the pre-established cutoff of three points. Rather, when subjected to an unplanned superiority analysis of Modafinil relative to Pitolisant, Modafinil therapy demonstrated a much greater reduction in the mean ESS score (difference of -2.75; $p < 0.002$).²⁰

Interestingly, Harmony III demonstrated a high participant drop-out of nearly 33%, with nearly 20% of those individuals citing “insufficient benefit.”²¹ However, among participants who completed the twelve-month treatment course, nearly 67% were deemed responders, with either an end-treatment ESS ≤ 10 or a reduction in ESS ≥ 3 ; the remaining 33% demonstrated a normalized ESS (i.e. ESS ≤ 10).²¹

PHASE III STUDIES

The P11-05 study (Harmony CTP) was a double-blind, randomized, parallel-group phase III study seeking to evaluate the effect of Pitolisant vs. placebo on the reduction in cataplectic episodes in narcoleptic patients, measured as the number of episodes per week.¹⁷ One hundred forty-four narcoleptic patients were divided into Pitolisant and placebo groups, each of which was given a seven-week treatment regimen, consisting of three weeks of flexible Pitolisant dosing (5, 10, or 20 mg daily) followed by four weeks of stable dosing (5, 10, 20, or 40 mg daily). The primary analysis demonstrated a significant reduction in cataplexy episodes for the Pitolisant group. Compared to baseline, the stable dosing period showed a reduction in cataplexy episodes per week from 9.15 to 3.28 in the Pitolisant group and 7.31 to 6.79 for the placebo group. Additionally, after Harmony CTP, the percentage of participants demonstrating a high rate of cataplectic episodes (defined as >15 episodes/week) was significantly higher in the placebo group (23.5%; 95% CI of 12 to 51) relative to the Pitolisant group (5.6%; 95% CI of 3 to 54). In evaluating Pitolisant’s effect on EDS, Harmony CTP demonstrated a significant reduction in mean ESS scores relative to placebo: Pitolisant group showed a change of -5.4 ± 4.3 ($p < 0.001$), while the placebo group showed a mean ESS score change of -1.9 ± 4.3 ($p < 0.001$).¹⁷

While data have yet to be fully published, the P10-01 study (Harmony IV)- the most recent RCT evaluating the effect of Pitolisant therapy on EDS relative to placebo, with add-on sodium oxybate- demonstrated no significant differences about daytime sleepiness (ESS score reduction), rates of cataplexy, or quality of life.²⁰ This study evaluated 48 narcoleptic patients receiving a 5 mg daily dose of Pitolisant, gradually increased to 40 mg daily during the first five weeks, followed by a steady daily dose for one month. Results demonstrated a mean EDS score change of -2.6 ($p = 0.595$) for Pitolisant and -2.1 ($p = 0.595$) for placebo group.²⁰

SAFETY

Setnik et al. devised a single dose, randomized, double-blind, active- and placebo-controlled, four sequences, four-period crossover study to evaluate abuse potential and overall clinical safety of Pitolisant for narcoleptic patients, with

or without, cataplexy.²² This study recruited only participants with a history of recreational stimulant use at least once in the past eight weeks or ten times in the past year. Researchers first screened participants based on their ability to discern a 60 mg Phentermine dose from placebo, randomly assigning the order in which each was received. Provided the participant could distinguish between the two correctly, they were assigned to one of four regimens in the double-blind treatment phase, differing only in order of dosing regimen, with a seven-day washout between each medication. Each participant received 35.6 mg Pitolisant, 213.6 mg Pitolisant, 60 mg Phentermine HCl, and a placebo. Participants were evaluated using the Drug Liking Visual Analog Scale (DLVAS), involving subjective rankings of each drug’s appeal to participants, with a score of 0 meaning “strong disliking” and a score of 100 meaning “strong liking.” Phentermine demonstrated a vastly higher DLVAS score when compared with placebo ($+22.7$; $p < 0.0001$), Pitolisant 35.6 mg ($+21.4$; $p < 0.0001$), and Pitolisant 213.6 mg ($+19.7$; $p < 0.0001$), suggesting a significant difference in addiction potential between Phentermine and Pitolisant. Compared to placebo, neither Pitolisant 35.6 mg nor Pitolisant 213.6 mg showed a difference in DLVAS score (0.0 with $p < 0.0001$; 0.0 with $p = 0.0013$, respectively). In terms of adverse effects, the most commonly reported side effects were headache (three participants in the placebo group, two in the Pitolisant 213.6 mg group) and vomiting (one in Pitolisant 35.6 mg group). However, these adverse effects appear to be dose-related, and it is important to note that no study participant withdrew from the study due to adverse side effects. All other recorded adverse effects were related to phentermine.²² A meta-analysis conducted by Lehert et al. examined 10 RCTs comparing the efficacy of Pitolisant relative to modafinil in cataplectic and non-cataplectic patients.²³ This was done by comparing ESS and MWT scores; differences in ESS and MWT scores were statistically insignificant, but, in cataplectic patients, results demonstrated Pitolisant superiority to Modafinil. Additionally, with a risk ratio of 0.86 ± 0.4 in favor of Pitolisant, there is evidence that Pitolisant is safer than Modafinil in treating narcolepsy.²³

Over the past few years, questions have been raised (notably by the International Conference on Harmonization (ICH) and the Comprehensive in vitro Pro-arrhythmia Assay (CiPA)) regarding Pitolisant’s inhibition of calcium and late I_{Na} ion channels, with concern that this could lead to prolonged QTc.²⁴ While non-clinical data presented by these groups certainly refutes this idea (especially at the standard 20 and 40 mg doses of Pitolisant), analysis by Ligneau et al. acknowledges the need for further study on Pitolisant’s effect on cardiac rhythm and other conditions that can predispose or contribute to QT prolongation.²⁴

CONCLUSION

Narcolepsy is a debilitating sleep disorder that presents with EDS and cataplexy in some patients. Pharmacologic treatment options include Modafinil and Armodafinil for EDS and sodium oxybate for cataplexy secondary to narcolepsy. Pitolisant, an antagonist/inverse agonist of H3R, is a novel drug currently used in Europe and United States

to treat EDS and cataplexy in narcolepsy. Clinical trials in phase II and phase III have shown mean ESS score decreases and reductions in cataplexy episodes in participants administered Pitolisant. Based on comparative studies, recent evidence has shown that Pitolisant is non-inferior to Modafinil in the treatment of EDS but superior to Modafinil in reducing cataplexy.^{23,25}

.....

LIST OF AUTHOR AND THEIR INDIVIDUAL CONTRIBUTIONS

Noeen S (MD, MPH), (study design, manuscript preparation, and editing)

David O, (study design, manuscript preparation)

Hannah H, (study design, manuscript preparation)

Mark A, (study design, manuscript preparation)

Elyse C, (study design, manuscript preparation)

Juyeon K, (study design, manuscript preparation)

Adam K (PharmD), (study design, manuscript preparation)

Alan K (MD, Ph.D.), (study design, manuscript preparation)

DISCLOSURES

The authors did not receive any funding or financial support or potential sources of conflict of interests.

Submitted: November 22, 2021 EDT, Accepted: January 11, 2022 EDT

Table 1. Clinical Efficacy and Safety

Study Name	Groups Studied and Intervention	Results and Findings	Conclusions
P05-03	22 participants were randomly assigned to Pitolisant and placebo regimens, each of which lasted seven days. Primary outcomes were measured using the Epworth Sleepiness Scale (ESS).	Participants saw a notable reduction in ESS scores from a baseline of 17.55±3.89 to 11.81±6.11. Pitolisant treatment represents a 4.86±5.12 reduction in ESS compared to placebo, and a 5.85±5.51 reduction relative to baseline.	Pitolisant demonstrates no statistically significant benefit over baseline.
P06-06	26 participants were administered varying doses of Pitolisant for a maximum of nine months to evaluate efficacy of escalated doses. Primary outcomes were measured using the ESS.	Participants received either 10, 20, or 40 mg daily doses for a maximum of nine months and were evaluated at one-, three-, and nine-month intervals. These regimens resulted in ESS score reductions of 4.8, 5.3, and 6.9 points, respectively.	The efficacy of Pitolisant is dose-dependent, suggesting 40 mg would demonstrate most therapeutic value.
Harmony I	95 participants from 32 centers across Europe were randomly assigned to either Pitolisant (n=32), Modafinil (n=33), or placebo (n=30) for eight weeks, to evaluate efficacy of Pitolisant relative to standard Modafinil therapy. Primary outcomes were measured using the ESS.	Treatment schedule over eight weeks: three weeks of flexible dosing (10, 20, or 40 mg/day of pitolisant; 100, 200, or 400 mg/day of modafinil) followed by five weeks of a steady dose of either Pitolisant or Modafinil. By the end of eight weeks, mean ESS score reductions were -3.4±4.2 for placebo, -5.8±6.2 for Pitolisant, and -6.9±6.2 for Modafinil.	No demonstration of Pitolisant's superiority relative to Modafinil.
Harmony Ibis	165 participants were divided randomly into Pitolisant (n=67), Modafinil (n=65), or placebo (n=33) groups to evaluate efficacy of Pitolisant relative to standard Modafinil therapy. Primary outcomes were measured using the ESS.	Flexible dosing for first three weeks of treatment: 10 or 20 mg daily of Pitolisant; or 100, 200, or 400 mg daily of Modafinil. Flexible treatment was followed by five weeks of stable dosing. The mean ESS score reductions follow the eight-week regimen: -3.6±5.6 for placebo, -4.6±4.6 for Pitolisant, and -7.8±5.9 for Modafinil. Difference in mean ESS scores of only -1.94 (95% CI of -4.005 to -0.07; p=0.06) between Pitolisant and placebo, thus failing to meet efficacy criterion of a difference of at least three ESS points. Non-inferiority of Pitolisant relative to Modafinil could not be established, as data demonstrate a difference of -2.75 (95% CI -4.48 to -1.02) which failed to meet the pre-established cutoff of three points	When subjected to an unplanned superiority analysis of Modafinil relative to Pitolisant, the Modafinil group demonstrated a much greater mean ESS score reduction. Thus, Pitolisant failed to demonstrate superiority to both placebo and Modafinil

<p>Harmony III</p>	<p>102 participants with narcolepsy, with or without cataplexy, were enrolled in an open-label trial, 68 of which completed a twelve-month treatment period. Primary endpoint was incidence of Treatment-Emergent Adverse Effects (TEAE) at twelve months, while secondary endpoints were measured using the (ESS).</p>	<p>Participants started with one week of 5 mg Pitolisant daily, followed by a week of 10 mg daily, followed by a week of 20 mg, subject to safety and tolerability. After a month, the investigator could titrate the dose to 40mg if lower doses were not deemed efficacious. Commonly-reported TEAEs were headache (11.8%), insomnia (8.8%), weight gain (7.8%), anxiety (6.9%), depressed mood (4.9%), and nausea (4.9%). Also reported were seven instances of severe adverse effects, all of which were deemed unrelated to Pitolisant therapy. Nearly 67% of those who finished the treatment regimen were deemed responders with either an end-treatment ESS \leq 10 or a reduction in ESS \geq 3, while the remaining 33% demonstrated a normalized ESS (i.e. ESS \leq 10).</p>	<p>The vast majority of TEAEs reported while on Pitolisant therapy were mild to moderate; only 6.55% were severe and related to the study drug. In terms of secondary goals, Pitolisant demonstrated a high response rate at therapeutic dosages.</p>
<p>Harmony CTP (P11-05)</p>	<p>145 narcoleptic participants were divided into Pitolisant and placebo groups, each of which was given a seven-week regimen consisting of three weeks of flexible Pitolisant dosing (5, 10, or 20 mg daily) followed by four weeks of stable dosing (5, 10, 20, or 40 mg daily). This study sought to evaluate the effect of Pitolisant versus placebo on reducing cataplectic episodes in narcoleptic patients, measured as the number of episodes per week. Secondary objectives evaluated the effect of Pitolisant on EDS, measured using the ESS.</p>	<p>When measured relative to the frequency of cataplexy during a two-week baseline period, the stable dosing period showed a reduction in episodes per week for the Pitolisant group from 9.15 to 3.28, and the placebo group from 7.31 to 6.79. At the study's conclusion, the percentage of participants demonstrating a high frequency of cataplectic episodes (defined as >15 episodes/week) was significantly higher in the placebo group (23.5%; 95% CI of 12 to 51) relative to the Pitolisant group (5.6%; 95% CI of 3 to 54). Harmony CTP demonstrated significant reduction in mean ESS scores relative to the placebo group. The placebo group showed a mean ESS score change of -1.9 ± 4.3 ($p < 0.001$) relative to baseline values, while the Pitolisant group exhibited a change of -5.4 ± 4.3 ($p < 0.001$).</p>	<p>There was a statistically significant reduction in cataplectic episodes in the Pitolisant group relative to placebo. Additionally, relative to placebo, Pitolisant showed a statistically significant reduction in overall EDS.</p>

REFERENCES

1. Morse AM. Narcolepsy in Children and Adults: A Guide to Improved Recognition, Diagnosis and Management. *Medical Sciences*. 2019;7(12):106. [doi:10.3390/medsci7120106](https://doi.org/10.3390/medsci7120106)
2. Kornum BR, Knudsen S, Ollila HM, et al. Narcolepsy. *Nat Rev Dis Primers*. 2017;3(1). [doi:10.1038/nrdp.2016.100](https://doi.org/10.1038/nrdp.2016.100)
3. Ruoff CM, Reaven NL, Funk SE, et al. High Rates of Psychiatric Comorbidity in Narcolepsy: Findings from the Burden of Narcolepsy Disease (BOND) Study of 9,312 Patients in the United States. *J Clin Psychiatry*. 2017;78(02):171-176. [doi:10.4088/jcp.15m10262](https://doi.org/10.4088/jcp.15m10262)
4. Scammell TE. Narcolepsy. *Campion EW, ed. N Engl J Med*. 2015;373(27):2654-2662. [doi:10.1056/nejmra1500587](https://doi.org/10.1056/nejmra1500587)
5. Sahni AS, Carlucci M, Malik M, Prasad B. Management Of Excessive Sleepiness In Patients With Narcolepsy And OSA: Current Challenges And Future Prospects. *Nat Sci Sleep*. 2019;11:241-252. [doi:10.2147/nss.s218402](https://doi.org/10.2147/nss.s218402)
6. Guevarra JT, Hiensch R, Varga AW, Rapoport DM. Pitolisant to Treat Excessive Daytime Sleepiness and Cataplexy in Adults with Narcolepsy: Rationale and Clinical Utility. *Nat Sci Sleep*. 2020;12:709-719. [doi:10.2147/nss.s264140](https://doi.org/10.2147/nss.s264140)
7. Thorpy MJ. Recently Approved and Upcoming Treatments for Narcolepsy. *CNS Drugs*. 2020;34(1):9-27. [doi:10.1007/s40263-019-00689-1](https://doi.org/10.1007/s40263-019-00689-1)
8. Won C, Mahmoudi M, Qin L, Purvis T, Mathur A, Mohsenin V. The Impact of Gender on Timeliness of Narcolepsy Diagnosis. *J Clin Sleep Med*. 2014;10(01):89-95. [doi:10.5664/jcsm.3370](https://doi.org/10.5664/jcsm.3370)
9. Scheer D, Schwartz SW, Parr M, Zgibor J, Sanchez-Anguiano A, Rajaram L. Prevalence and incidence of narcolepsy in a US health care claims database, 2008–2010. *Sleep*. 2019;42(7). [doi:10.1093/sleep/zsz091](https://doi.org/10.1093/sleep/zsz091)
10. Ohayon MM, Black J, Lai C, Eller M, Guinta D, Bhattacharyya A. Increased Mortality in Narcolepsy. *Sleep*. 2014;37(3):439-444. [doi:10.5665/sleep.3470](https://doi.org/10.5665/sleep.3470)
11. Ollila HM. Narcolepsy type 1: what have we learned from genetics? *Sleep*. 2020;43(11). [doi:10.1093/sleep/zsaa099](https://doi.org/10.1093/sleep/zsaa099)
12. Kawai M, O'Hara R, Einen M, Lin L, Mignot E. Narcolepsy in African Americans. *Sleep*. 2015;38(11):1673-1681. [doi:10.5665/sleep.5140](https://doi.org/10.5665/sleep.5140)
13. Mahoney CE, Cogswell A, Koranik IJ, Scammell TE. The neurobiological basis of narcolepsy. *Nat Rev Neurosci*. 2019;20(2):83-93. [doi:10.1038/s41583-018-0097-x](https://doi.org/10.1038/s41583-018-0097-x)
14. Kumar S, Sagili H. Etiopathogenesis and Neurobiology of Narcolepsy: A Review. *J Clin Diagn Res*. 2014;8(2). [doi:10.7860/jcdr/2014/7295.4057](https://doi.org/10.7860/jcdr/2014/7295.4057)
15. *Narcolepsy Fact Sheet | National Institute of Neurological Disorders and Stroke*. Accessed September 6, 2021. <https://www.ninds.nih.gov/Disorders/Patient-Caregiver-Education/Fact-Sheets/Narcolepsy-Fact-Sheet>
16. Benca RM. Narcolepsy and Excessive Daytime Sleepiness: Diagnostic Considerations, Epidemiology, and Comorbidities. *The Primary Care Companion for CNS Disorders*. 2007;9(Suppl 2: Editor Choice):0-0. Accessed September 6, 2021. <https://www.psychiatrist.com/pcc/sleep/narcolepsy-excessive-daytime-sleepiness-diagnostic>
17. Pérez-Carbonell L, Leschziner G. Clinical update on central hypersomnias. *J Thorac Dis*. 2018;10(S1):S112-S123. [doi:10.21037/jtd.2017.10.161](https://doi.org/10.21037/jtd.2017.10.161)
18. Morrison I, Riha RL. Excessive daytime sleepiness and narcolepsy – an approach to investigation and management. *Eur J Intern Med*. 2012;23(2):110-117. [doi:10.1016/j.ejim.2011.09.005](https://doi.org/10.1016/j.ejim.2011.09.005)
19. Abad V, Guilleminault C. New developments in the management of narcolepsy. *Nat Sci Sleep*. 2017;9:39-57. [doi:10.2147/nss.s103467](https://doi.org/10.2147/nss.s103467)
20. Romigi A, Vitrani G, Lo Giudice T, Centonze D, Franco V. Profile of pitolisant in the management of narcolepsy: design, development, and place in therapy. *Drug Des Devel Ther*. 2018;12:2665-2675. [doi:10.2147/dddt.s101145](https://doi.org/10.2147/dddt.s101145)
21. 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). [doi:10.1093/sleep/zsz174](https://doi.org/10.1093/sleep/zsz174)
22. Setnik B, McDonnell M, Mills C, et al. Evaluation of the abuse potential of pitolisant, a selective H3-receptor antagonist/inverse agonist, for the treatment of adult patients with narcolepsy with or without cataplexy. *Sleep*. 2020;43(4). [doi:10.1093/sleep/zsz252](https://doi.org/10.1093/sleep/zsz252)

23. Lehert P, Szoeki C. Comparison of modafinil and pitolisant in narcolepsy: a non-inferiority metaanalytical approach. *Drugs Context*. 2020;9. doi:10.7573/dic.2020-6-2

24. Ligneau X, Shah RR, Berrebi-Bertrand I, et al. Nonclinical cardiovascular safety of pitolisant: comparing International Conference on Harmonization S7B and Comprehensive *in vitro* Proarrhythmia Assay initiative studies. *Br J Pharmacol*. 2017;174(23):4449-4463. doi:10.1111/bph.14047

25. Barateau L, Dauvilliers Y. Recent advances in treatment for narcolepsy. *Ther Adv Neurol Disord*. 2019;12. doi:10.1177/1756286419875622