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APPLICATION NUMBER:

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CLINICAL REVIEW(S)

CLINICAL REVIEW

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Division/Office	Division of Psychiatry/Office of Neuroscience
Reviewer Name(s)	Martine Solages, MD
Review Completion Date	September 28, 2020
Established/Proper Name	Pitolisant
(Proposed) Trade Name	Wakix
Applicant	Harmony Biosciences
Dosage Form(s)	4.45 mg and 17.8 mg film-coated tablets
Applicant Proposed Dosing Regimen(s)	17.8 to 35.6 mg daily
Applicant Proposed Indication(s)/Population(s)	Cataplexy in adult patients with narcolepsy
Recommendation on Regulatory Action	Approval
Recommended Indication(s)/Population(s) (if applicable)	Treatment of cataplexy in adult patients with narcolepsy

1. Background

Pitolisant is a histamine 3 (H3) receptor antagonist and inverse agonist. Pitolisant purportedly inhibits the negative feedback mechanism for histamine, resulting in increased histamine release. Pitolisant may also stimulate release of histamine from presynaptic neurons and facilitate histamine synthesis. In addition, its actions on the H3 receptors are thought to lead to downstream release of dopamine, noradrenaline, and acetylcholine.

Pitolisant received European Medicines Agency (EMA) authorization in 2016 for the treatment of narcolepsy with and without cataplexy and is marketed in Europe under the trade name Wakix. The Agency granted Orphan Drug Designation to pitolisant in March 2010. In April 2018, the cataplexy development program received fast track and breakthrough therapy designation. Fast track designation was granted for the treatment of excessive daytime sleepiness (EDS) in narcolepsy, but breakthrough therapy designation was denied. Rolling review status was granted in June 2018. The new drug application (NDA) was granted priority review. Pitolisant received FDA approval for the treatment of EDS in adult patients with narcolepsy in August 2019 (NDA 211150, trade name Wakix). However, a Complete Response Letter was issued for the cataplexy indication.

The Applicant submitted two phase 3 studies in support of the cataplexy indication—HARMONY CTP (P11-05) and HARMONY 1 (P07-03).

HARMONY CTP (P11-05) was a phase 3, randomized, double-blind, placebo-controlled trial to assess the safety and efficacy of pitolisant for the treatment of cataplexy attacks and excessive daytime sleepiness in narcolepsy. The study was conducted at 16 sites in 9 countries (Bulgaria, Macedonia, Hungary, Serbia, Turkey, Czech Republic, Poland, Russia, and Ukraine). Patients aged 18 or older who met criteria for narcolepsy with cataplexy based on the International Classification of Sleep Disorders–Second Edition (ICSD-2), had experienced at least 3 weekly cataplexy attacks for 1 month, and scored ≥ 12 on the Epworth Sleepiness Scale were eligible to be enrolled. 54 patients were randomized to receive pitolisant and 52 patients were randomized to receive placebo. Pitolisant had a statistically significant effect ($p < 0.0001$) on the change in the average number of cataplectic events per week (i.e., weekly rate of cataplexy; WRC) from baseline to the end of the study.

HARMONY I (P07-03) was a phase 3, randomized, double-blind, placebo- and modafinil-controlled trial to assess the safety and efficacy of pitolisant for the treatment of excessive daytime sleepiness in narcolepsy. The study was conducted at sites in France, Germany, Hungary, the

Netherlands, and Switzerland. Patients aged 18 or older who met ICDS-2 criteria for narcolepsy and who scored ≥ 14 on the Epworth Sleepiness Scale (ESS) were eligible to be enrolled. Patients with and without cataplexy were included. 95 patients were randomized: 32 to pitolisant, 30 to placebo, and 33 to modafinil. Pitolisant demonstrated statistically significantly greater improvement on the primary endpoint, the least square mean final ESS score, compared to placebo.

The rate of daily cataplectic events was a secondary endpoint in HARMONY 1. In the analysis that was submitted to the original NDA, the Applicant found that pitolisant-treated patients (in the subgroup of patients with cataplexy) had significantly fewer daily cataplectic events ($p = 0.034$) when participants with zero or missing cataplectic events were imputed. The Agency's biometric review noted that when subjects with zero or missing cataplectic events were ignored, pitolisant did not demonstrate a statistically significant improvement in daily rates of cataplexy over placebo.

As noted in the Complete Response Letter, the Agency determined that HARMONY 1 could not be considered an adequate and well-controlled trial for the cataplexy endpoint for the following reasons:

- Cataplexy was a secondary endpoint in HARMONY 1. There was no prospective plan to control the type 1 error rate for secondary endpoints in this study.

- The subgroup of interest was defined post hoc based on event(s) that occurred post-randomization, which violates the randomization principle and could lead to invalid conclusions.

- The statistically significant finding for cataplexy in HARMONY 1 was dependent on how missing values were handled (i.e., missing or zero values were assigned a value of 0.5; if they were excluded from the analysis, the treatment effect was no longer statistically significant).

The Agency considered HARMONY CTP a positive, adequate, and well-controlled trial for the cataplexy indication. Although the Agency may grant approval based on a single study with confirmatory evidence in certain circumstances, the Agency determined that HARMONY CTP did not meet the criteria for a study that could, by itself, provide evidence of effectiveness. The Agency noted the small size of the study (N=105), the fact that the study was conducted exclusively in Eastern Europe and that race and ethnicity were not reported, and that < 10 % of patients were elderly. The Agency noted that two positive trials have been required in other narcolepsy development programs. The Agency advised that a second trial, substantiating the results of HARMONY CTP, would be required to obtain the cataplexy indication. The Agency

recommended that the substantiating study be a randomized, double-blind, placebo-controlled, fixed-dose trial of pitolisant for cataplexy that enrolls a meaningful fraction of U.S. patients.

A Type A post-action meeting to discuss the scientific issues raised in the Complete Response Letter was held on December 12, 2019. The Applicant acknowledged the Agency's concerns about the statistical analysis plan for HARMONY 1, but made the case that the statistical significance of the results would stand regardless of analysis strategy. The Applicant also presented the view that HARMONY CTP was adequately powered and that the study results could be generalizable to the U.S. population despite the concerns about the demographic characteristics of the study population raised by the Agency.

Following the Type A meeting, the Agency reviewed the Type A briefing documents and re-analyzed the HARMONY 1 data. On June 25, 2020, the Agency issued a General Advice Letter recommending that the Applicant submit a complete response resubmission.

The Applicant has submitted a complete response to the CR letter, including a discussion of all the deficiencies outlined in the CR letter, a safety update, and revised labeling.

In the complete response, the Applicant disagreed with Agency's assessment of the limitations of the HARMONY CTP study. The Applicant made the case that the study was adequately sized and powered, as evidenced by a p value of < 0.0001 on the primary efficacy endpoint. The Applicant referred to an analysis of dose response by region and its white paper (b) (4) and maintained that geography and race did not impact the study results. Finally, the Applicant noted that pharmacokinetic studies did not show differences in absorption, distribution, metabolism, or excretion in elderly patients. The Applicant did not submit any new data regarding the HARMONY CTP study. Despite the limitations outlined in the CR letter, the Agency considered HARMONY CTP a positive study for the cataplexy indication. Therefore, the primary focus of this review is whether HARMONY 1 can provide substantiating evidence for the cataplexy indication and whether any new safety signals that would impact the benefit:risk determination have emerged in the postmarketing period.

The re-analysis of the HARMONY 1 efficacy data and the safety update are discussed below.

2. Re-analysis of Efficacy Data

Please see the Biometrics review by Dr. Semhar Ogbagaber for a full description of the re-analysis of the efficacy data. In the CR letter, the Agency identified three primary reasons that HARMONY 1 was not considered an adequate and well controlled trial for the cataplexy endpoint: the statistically significant finding depended on how missing data were handled; the cataplexy

subgroup was defined post hoc based on events that occurred post-randomization; and the frequency of cataplexy attacks was not a type 1-error-controlled endpoint.

During the Type A post-action meeting and in the briefing materials, the Applicant noted that the original statistical analysis plan (from November 2010) included a plan for analysis of the frequency of cataplexy attacks using the Poisson regression. However, because of human error, subsequent submissions analyzed the cataplexy data using a t-test. The Applicant made the case that, had the originally planned Poisson regression been used, the statistical significance of the results would not have depended on how missing data were handled.

In addition, the Applicant presented all possible clinically relevant definitions of the cataplexy subgroup (full analysis set, cataplexy experienced at baseline, cataplexy experienced during the whole trial, cataplexy experience reported in the past) and found that the results remained statistically significant.

The Applicant acknowledged that the statistical analysis plan did not include a prespecified plan to control for type 1 error for the cataplexy endpoint. However, the Applicant applied multiplicity adjustments including: Bonferroni method (most conservative); Holm stepdown procedure; Hochberg step-up procedure; fixed-sequence statistical strategy; fallback method; serial gatekeeping strategy; parallel gatekeeping strategy; and truncated Holm procedure for parallel gatekeeping. The Applicant found that the study results satisfied all these methods.

Dr. Ogbagaber re-analyzed the data and confirmed the Applicant's findings. With the identified deficiencies resolved, the Agency has determined that HARMONY 1 can serve as substantiating evidence of effectiveness for the cataplexy indication.

3. Safety Update

3.1. Clinical Studies and Programs Included in the Safety Update

The data cutoff was March 31, 2018, for the original NDA and February 12, 2019, for the 120-day safety update. The Sponsor has submitted a safety update that includes data generated from clinical studies and clinical programs since the original NDA review. The safety update also includes postmarketing data from the United States (from November 4, 2019, to May 13, 2020) and Europe (from February 13, 2019, to March 31, 2020).

Data from the following narcolepsy studies and clinical programs were considered in the safety update (Table 1):

Table 1: Narcolepsy Studies and Clinical Programs

Study Number	Description	Status	Location	Enrollment
HBS-101-CL-001	U.S. Expanded Access Program	Completed; closed February 2020	United States	639 adult patients with narcolepsy; 622 received at least one dose of pitolisant
P11-06	Randomized, double-blind, placebo-controlled efficacy and safety study in pediatric patients with cataplexy	Ongoing (data blinded)	Europe	85 patients (out of an anticipated 96 patients) have been randomized
P15-11	European Post-Authorization Safety Study	Ongoing	Europe	370 patients have enrolled
N/A	European Compassionate Use Program (CUP)	Ongoing (in Spain only); expected to close September 2020	Europe	298 patients have received pitolisant through this program

Source: Adapted from Applicant's Safety Update, Table 2, pages 11–14.

Data from the following studies in indications other than narcolepsy were considered (Table 2):

Table 2: Clinical Studies in Non-Narcolepsy Indications

Study Number	Description	Status	Location	Enrollment
P15-13	Phase 3 efficacy and safety study (with open-label extension) in adult patients with obstructive sleep apnea (OSA	Ongoing	Europe	361 (out of an anticipated 400) have been enrolled
HBS-101-CL-003	Pharmacokinetic study in pediatric patients with Prader-Willi Syndrome (PWS)	Completed	United States	Eight patients enrolled in and completed the study
HBS-101-CL-004	Open-label safety extension study in pediatric patients with PWS who completed HBS-101-CL-003	Ongoing	United States	The eight patients who completed HBS-101-CL-003 are enrolled in the open-label extension

Source: Adapted from Applicant's Safety Update, Table 2, pages 11–14.

3.2. Treatment-Emergent Adverse Events

Treatment-emergent adverse event (TEAE) data were provided for the completed U.S. Expanded Access Program (HBS-101-CL-001), the completed PK study in pediatric patients with PWS (HBS-101-CL-003), and the ongoing open-label extension in pediatric patients with PWS (HBS-101-CL-004). Data for the ongoing efficacy and safety studies in pediatric narcolepsy and obstructive sleep apnea remain blinded, so adverse event data by treatment-group are not available for these studies. The Applicant submitted updated serious adverse event (SAE) data for the ongoing European post-marketing safety study (P15-11) and the CUP.

HBS-101-CL-001: U.S. Expanded Access Program (EAP)

The EAP was initiated on March 31, 2018. The data cutoff for EAP data was August 10, 2018, for the original NDA and February 2, 2019, for the 120-day safety update. At the time of the 120-day safety update, 366 patients had received pitolisant through this program. The EAP closed on February 24, 2020. A total of 639 patients enrolled and 622 patients received at least one dose, and 278 completed the program.

Of the 344 patients who discontinued treatment, the most common reasons for treatment discontinuation were adverse events (21.4%) and lack of effect (20.3%). Other reasons for discontinuation included lost to follow-up, treatment nonadherence, and withdrawal of consent. The most frequent treatment-emergent adverse events (TEAEs) leading to discontinuation were headache, anxiety, insomnia, and nausea.

Table 3 lists the most common treatment-emergent adverse events (TEAEs) reported in the EAP.

Table 3: Treatment-Emergent Adverse Events (TEAEs) Occurring in **≥2%** of Patients in the U.S. Expanded Access Program

Preferred Term	TEAEs in Treated Patients N=622 n (%)
Headache	70 (11%)
Nausea	43 (7%)
Anxiety	40 (6%)
Insomnia	36 (6%)
Dizziness	15 (2%)
Depression	15 (2%)
Fatigue	14 (2%)
Irritability	13 (2%)

Source: Adapted from Applicant's Safety Update, Table 7, page 20.

Headache, nausea, anxiety, insomnia, dizziness, and irritability were observed in ≥ 2% of patients in the phase 3 narcolepsy studies submitted in the original NDA and are listed in the adverse reaction table in the Prescribing Information. Depression and fatigue are listed in the Prescribing Information as adverse reactions that have been observed in the postmarketing period.

HBS-101-CL-003: Pharmacokinetic Study in Pediatric Patients with PWS

A total of eight patients completed study HBS-101-CL-003, "An Open-Label, Phase 1 Study to Assess the Steady State Pharmacokinetics of Pitolisant in a Predefined Population of Pediatric Patients with Prader-Willi Syndrome." TEAEs of nasopharyngitis (two patients), upper respiratory infection (one patient), and hepatic enzyme increased (one patient) were reported. The patient who experienced hepatic enzyme elevation recovered after an over-the-counter supplement was discontinued.

HBS-101-CL-004: Open-Label Extension in Pediatric Patients with PWS

A 16-year-old female reported adverse events of influenza, vomiting, and seizure. The patient's medical history included PWS, hypotonia, hip dysplasia, scoliosis, hypogonadism, adrenal insufficiency, narcolepsy, and anxiety. Concomitant medications included somatropin, prednisone, estradiol, norethindrone, methylphenidate, and citalopram. The patient had been receiving pitolisant 17.8 mg since 2017 through the FDA personal importation program. The patient developed influenza symptoms on (b) (6), and reported vomiting on (b) (6). She was treated with oseltamivir. On the same day, she experienced a possible seizure event (loss of consciousness, pallor, diaphoresis, and involuntary muscle twitching lasting 15 to 20 seconds). No diagnostic tests were conducted. Treatment with pitolisant was uninterrupted. No further suspected seizure events were reported. The Investigator also considered the possibilities that the event was a syncopal episode or that it was related to oseltamivir. The Investigator assessed the event as unrelated to pitolisant.

Of note, in the nonclinical program, convulsions occurred when rats, mice, and dogs were exposed to high-dose pitolisant. No seizures were observed in the controlled narcolepsy clinical studies, but have been reported in the European post-marketing database. Epilepsy is listed in Section 6.2 of the Prescribing Information (Postmarketing Experience). In this case, the suspected seizure event occurred after initiation of pitolisant, occurred in the context of acute illness, and resolved without interruption of pitolisant.

Reviewer Comment: The most commonly observed treatment-emergent adverse events that have been observed in U.S. patients are already listed in pitolisant labeling. Seizure events were an adverse event of special interest in the original NDA review because of convulsions in nonclinical studies. One patient in the PWS development program reported an adverse event of seizure. However, this patient had tolerated pitolisant at the same dose for years prior to the event and the reported seizure occurred in the context of an acute infection, which suggests that the event was unlikely to be related to pitolisant. No changes to Section 6 of labeling based on the updated TEAE data are recommended.

3.3. Deaths

At the time of the 120-day safety update, nine deaths had occurred in the pitolisant development program, including one death in the narcolepsy development program (Table 4).

Table 4: Deaths in the Pitolisant Development Program (All Indications) by 120-Day Safety Update

Participant Number	Clinical Trial	Indication	Treatment	Description
(b) (6)	P09-10	Narcolepsy	pitolisant	73-year-old female with narcolepsy. Enrolled in open-label extension for 10 months when found dead at home. No autopsy performed. Investigator thought patient death could be related to hot weather conditions.
	P06-11	Parkinson's disease	pitolisant	73-year-old male with Parkinson's disease. Enrolled in open-label extension for 5 months when hospitalized for bronchopneumopathy. Died 7 days after admission.
	P06-11	Parkinson's disease	pitolisant	80-year-old male with Parkinson's disease. Enrolled in open-label extension for 9 months when hospitalized for aspiration with asphyxia. Died the day after admission.
	P09-09	OSA	pitolisant	53-year-old male with history of obstructive sleep apnea, hypertension, type II diabetes mellitus, chronic obstructive pulmonary disease, and obesity. Enrolled in open-label extension for 7 months when died at home after reporting dyspnea and abdominal discomfort. No autopsy.
	P09-09	OSA	pitolisant	58-year-old male with history of obstructive sleep apnea, hypertension, atrial fibrillation, osteoarthrosis, obesity, and metabolic syndrome. Found dead at home 2.5 months after the initiation of treatment. No autopsy was performed. Cause of death reported as acute cardiac and pulmonary insufficiency with concomitant severe OSA without continuous positive airway pressure (CPAP).
	P04-08	Schizophrenia	pitolisant	39-year-old male with history of schizophrenia, depressive episodes, prior suicide attempts. Found dead at home 2 months after randomization. Several empty boxes of medication were found.
	P15-13	OSA	pitolisant	64-year-old female with history of pneumonia, hypertension, asthma, chronic obstructive pulmonary disease, and obesity. Went into cardiac and respiratory arrest 4 days after starting pitolisant in open-label extension. No autopsy was performed. Physician diagnosis of stroke per patient's family.
	P05-08	Dementia	pitolisant	79-year-old female with Lewy Body Dementia. Completed the study and died 1 year later. Cause of death listed as disease progression.

Participant Number	Clinical Trial	Indication	Treatment	Description
(b) (6)	P05-08	Dementia	pitolisant	71-year-old male with Lewy Body Dementia, prior hospitalizations for confusional state and motor deficit, hallucinations, agitation, and aggression. Died 31 days after discontinuing pitolisant in open-label extension phase. Prior to death, had been hospitalized for pneumopathy with dysphagia. Cause of death listed as acute respiratory distress syndrome.

Source: FDA Clinical Review, NDA 211150, August 14, 2019, Table 35, page 76.
[a]Deaths occurred > 30 days after last date of study drug administration

The Applicant has provided case narratives for four additional deaths that have occurred since the 120-day safety update. One death was reported in the U.S. EAP, one death was reported in Study P15-11 (the European Post-Authorization Safety Study), and two deaths were reported in the Study P15-13 (the ongoing phase 3 efficacy and safety study in patients with OSA).

- (b) (6) **(EAP):** A 38-year-old male patient with a medical history of narcolepsy, bipolar disorder, epilepsy, and migraine died by suicide. The patient started pitolisant on (b) (6) and was receiving a dose of 35.6 mg. The patient was concomitantly prescribed valproate, dextroamphetamine-amphetamine, venlafaxine, sodium oxybate, and aripiprazole. On (b) (6) the patient reported a relapse of bipolar disorder and was involuntarily admitted to a psychiatric unit after placing a rope around his neck. While hospitalized, the patient's psychiatric medications were adjusted. The patient recovered and was discharged on (b) (6) Pitolisant treatment was continued. The case narrative indicates that the patient had been "doing well" throughout (b) (6). The patient received his last 30-day supply of pitolisant on (b) (6), and did not respond to outreach by the site during (b) (6) In a voicemail on (b) (6), the patient indicated that his last dose of pitolisant had been on (b) (6), and that he planned on receiving pitolisant through the commercial business program. On (b) (6), the patient hanged himself. The Investigator subsequently learned that the patient had experienced life stressors around the time of his death, including the loss of his job and separation from his wife. The Investigator assessed the event as unrelated to pitolisant.

- **Patient** (b) (6) A 61-year-old male patient with a medical history of narcolepsy, sleep apnea, diabetes, hypertension, and overweight died of pulmonary edema. The patient began receiving pitolisant on (b) (6), and was receiving a dose of 35.6 mg. The patient's concomitant medications included venlafaxine, modafinil, clonazepam, metformin, and nebivolol. Death occurred on (b) (6). No autopsy was performed. The Investigator assessed the event as unrelated to pitolisant.

- [redacted]: Sudden death was reported in a 63-year-old male with a medical history of obstructive sleep apnea, New York Heart Association Class II heart failure, hypertension, diabetes, metabolic syndrome, and obesity. Concomitant medications included amlodipine, telmisartan, tamsulosin, furosemide, metformin, gliclazide, allopurinol, and clopidogrel. The patient completed the double-blind treatment phase (data remain blinded) and entered the open-label extension on [redacted]. Pitolisant was titrated to 35.6 mg. ST segment depression was noted on electrocardiogram on [redacted], and assessed as not clinically significant. The patient died in his sleep on [redacted] No adverse events had been reported during the study. No autopsy was performed. The Investigator assessed the event as not related to pitolisant.

- [redacted]: Sudden death was reported in a 43-year-old female with a medical history of obstructive sleep apnea and obesity. No concomitant medications were reported. The patient completed the double-blind treatment period and entered the open-label extension on [redacted]. Pitolisant was titrated to a dose of 35.6 mg. The patient died suddenly at home on [redacted]. The patient had not reported any adverse events during the study. The patient reportedly had a visit with her primary care physician one month prior to her death during which complained of back pain. The was advised to lose weight and quit smoking at that time. The Investigator assessed the event as not related to pitolisant.

Reviewer Comment: Since the original NDA review, two deaths have occurred in pitolisant-treated patients with narcolepsy. The patient who died by suicide had previously experienced a relapse of bipolar disorder symptoms a month after initiating treatment with pitolisant. However, he reportedly recovered from the exacerbation of bipolar symptoms and continued pitolisant treatment without complications for almost 1 year afterwards. The suicide occurred in the context significant life stressors. The information in the case narrative does not suggest a clear link between pitolisant treatment and the suicide. The second patient died of pulmonary edema. The patient had other co-occurring conditions that could have plausibly increased the risk of developing pulmonary edema. No clear association between pitolisant and pulmonary edema is apparent in this narrative.

Two additional deaths occurred in patients in the OSA development program; a total of 5 deaths have occurred in the OSA program. Although these patients had co-morbid health conditions that could have contributed to their risk of death and although patients with OSA have a higher risk of sudden death, an association with pitolisant cannot be ruled out based on the available data. Most of the deaths occurred in uncontrolled, open-label extension trials that do not allow for a comparison with patients not receiving pitolisant. The data from the ongoing controlled study

(P15-13) in patients with OSA are blinded, so it is unknown whether pitolisant-treated patients with OSA experienced adverse events or clinical changes that could predispose to sudden death (e.g., electrocardiogram abnormalities, increased risk of cardiovascular or respiratory events). Of note, cardiac, vascular, and pulmonary adverse events have not been reported frequently in the postmarketing period (see Postmarketing Data), either in the United States or in Europe (where pitolisant has been available for more than 4 years). A thorough QT (TQT) study submitted to the original NDA did not find a clinically significant QTc prolonging effect with the recommended pitolisant dose, but a dose of 106.8 mg was associated with QTc prolongation of approximately 10 milliseconds. Most patients who receive pitolisant are unlikely to reach exposures seen with the 106.8 mg dose, as the highest recommended dose is 35.6 mg once daily. However, patients with hepatic or renal insufficiency, patients who are taking concomitant medications that interfere with CYP2D6 metabolism, and patients who are poor metabolizers of CYP2D6 may experience higher exposures without the dose adjustments recommended in labeling. Once completed, Study P15-13 may provide information about any specific safety considerations in the OSA population.

3.4. Serious Adverse Events

The Applicant has submitted updated serious adverse event (SAE) data from the EAP (HBS-101-CL-001), European post-authorization study (P15-11), the ongoing efficacy and safety study in pediatric patients with narcolepsy (P11-06), and the ongoing study in patients with obstructive sleep apnea (P15-13). No serious adverse events have been reported in European compassionate use program for patients with narcolepsy or in the PWS development program.

HBS-101-CL-001: U.S. Expanded Access Program (EAP)

At the time of the 120-day safety update, five patients had reported the following SAEs in the development program: meningitis and lymphoma, sepsis, alcoholic relapse, suicide attempt, and bipolar I disorder. The patient who reported bipolar I disorder subsequently died by suicide (please see case narrative above). Table 5 lists the additional SAEs that have been reported in 10 patients in the EAP since the 120-day safety update.

Table 5: Serious Adverse Events (SAEs) in the U.S. Expanded Access Program Post 120-Day Safety Update

Patient Number	Age/Gender	SAE
(b) (6)	64-year-old female	breast cancer, thymoma
	76-year-old male	pulmonary embolism, gait disturbance
	33-year-old female	suicidal ideation
	42-year-old male	myocardial infarction
	54-year-old female	vertigo

Patient Number	Age/Gender	SAE
(b) (6)	53-year-old female	breast cancer, stage IV
	48-year-old female	pulmonary embolism
	67-year-old male	pyelonephritis
	56-year-old male	dyspnea, urinary tract infection, hematuria
	37-year-old female	abortion spontaneous

Source: Applicant's Safety Update, Section 2.1, Serious Adverse Events from the Expanded Access Program, pages 63–75.

The case narrative for the patient who reported an SAE of abortion spontaneous is described below, under Pregnancies.

Suicidal ideation was reported as an SAE in a 33-year-old female with narcolepsy, post-traumatic stress disorder, and atypical bipolar disorder. The patient had a reported prior history of suicidal ideation and a suicide attempt. Concomitant medications included modafinil, venlafaxine, lamotrigine, clonazepam, prazosin, and estradiol/levonorgestrel. The patient began treatment with pitolisant on (b) (6). The patient reported increased anxiety after initiation of pitolisant. On (b) (6) she reported suicidal ideation. Her psychiatrist prescribed olanzapine and pitolisant was discontinued. Anxiety and suicidal ideation resolved within 48 hours of pitolisant discontinuation. The Investigator assessed this event as probably related to pitolisant. Suicidal ideation is listed in Section 6.2 of the Prescribing Information.

No clear association to pitolisant was evident in the case narratives of the other SAEs. Two patients reported SAEs of pulmonary embolism. Patient (b) (6) had potentially predisposing pre-existing medical conditions including obesity and coronary artery disease. In addition, developed pulmonary embolism 2 days after diagnosis of right lower extremity cellulitis, which may be associated with deep vein thrombosis. Patient (b) (6) was concurrently treated with estrogen when pulmonary embolism occurred. A signal for pulmonary embolism events has not emerged from postmarketing data or other pitolisant studies. The Investigator assessed gait disturbance in Patient (b) (6) as possibly related to pitolisant. However, during a neurology consultation, the patient was found to have continued taking multiple medications that had previously been discontinued because of a misunderstanding of the patient instructions. Pitolisant was considered as one of the possible contributing medications and was discontinued.

P15-11: European Post-Authorization Safety Study

The following SAEs were reported in Study P15-11 since the NDA review: seizure, hypertension, intervertebral discitis, ovarian cyst, colon cancer (each reported in one patient), and suicide attempt (two patients).

As noted above, seizure is an adverse event of special interest given the occurrence of convulsions in multiple species in nonclinical studies. The patient who reported the SAE of seizure is a 33-year-old female with a prior history of temporal lobe epilepsy and sleep-related hypermotor epilepsy. She experienced an increase in seizure frequency after starting pitolisant. Both positive de-challenge and re-challenge were reported and the Investigator assessed the events as related to pitolisant. Epilepsy is listed in Section 6.2 of the Prescribing Information.

Suicide attempt is also listed in Section 6.2 of the Prescribing Information. The two patients who made suicide attempts during the study continued treatment with pitolisant and recovered. The suicide attempts were assessed by the Investigator as unrelated to pitolisant.

P11-06: Efficacy and Safety Study in Pediatric Patients with Narcolepsy

The following SAEs were reported in Study 11-06: appendicitis and alcohol poisoning (each reported in one patient). Both events were assessed as unrelated to pitolisant.

P15-13: Efficacy and Safety Study in Adult Patients with Obstructive Sleep Apnea

At the time of the 120-day safety update, two SAEs had been reported in Study P15-13 (non-Hodgkin's lymphoma and bacterial skin infection). Two additional SAEs (in two patients)—respiratory infection and chronic obstructive pulmonary disease—have since been reported. These events were assessed by the Investigator as unrelated to pitolisant.

Reviewer comment: *No consistent pattern or safety signal emerged in review of the SAEs. The reported SAEs that appeared plausibly related to pitolisant–suicidal ideation and seizure–are labeled in Section 6 of the Prescribing Information.*

3.5. Pregnancies

Three pregnancies have been reported in the EAP since the 120-day safety update.

One patient who reported a pregnancy had enrolled in the EAP but had not yet initiated treatment with pitolisant.

Another patient discontinued pitolisant when she learned of the pregnancy (at approximately 5 weeks gestation). The pregnancy was reportedly uncomplicated. The patient delivered a full-term neonate. Delivery was complicated by nuchal cord and meconium in the amniotic fluid. The neonate had distress at birth requiring an overnight admission to the neonatal intensive care unit, but subsequently recovered and has had no further complications.

The third pregnancy ended in spontaneous fetal demise. The patient is 37-year-old female with prior history one spontaneous abortion and one live birth via caesarian section. The patient discontinued pitolisant at 10 weeks gestation when she learned of the pregnancy. Fetal demise occurred at 19 weeks gestation. On autopsy, the fetus was small and immature for gestational age. The placenta was fragmented. Histologic evidence of vascular malperfusion of the placenta was found. Karyotyping revealed an inversion of chromosome 9 that has reportedly been described as a normal variant. The Investigator assessed the event as related to pitolisant because it was the only medication the patient received during pregnancy. The company considered the event unrelated to pitolisant.

No pregnancies have been reported in the U.S. postmarketing database and no additional pregnancies have been reported in the European postmarketing database. A pregnancy identified in the European postmarketing database that was ongoing at the time of the original NDA submission resulted in the full-term birth of a healthy infant.

Reviewer comment: The data regarding the use of pitolisant in pregnancy are limited. The three new reported cases do not provide additional information that would require a change in labeling. The following studies are outstanding Postmarketing Requirements (PMRs):

- *A prospective, registry based observational exposure cohort study that compares the maternal, fetal, and infant outcomes of women exposed to pitolisant during pregnancy to an unexposed control population.*

- *An additional pregnancy study that uses a different design from the Pregnancy Registry (for example a case control study or a retrospective cohort study using claims or electronic medical record data with outcome validation)*

- *A lactation study in lactating women who have received therapeutic doses of pitolisant using a validated assay to assess concentrations of pitolisant in breast milk.*

3.6. Postmarketing Data

Pitolisant was authorized in the European Union on March 31, 2016. The Applicant reports that there have been (b) (4) patient-years of exposure as of March 31, 2020.

Pitolisant was approved in the United States on August 14, 2019, and became available commercially on November 4, 2019. Pitolisant is dispensed through specialty pharmacies. To date, (b) (4) unique patients have received pitolisant in the United States.

U.S. Postmarketing Data

A total of 65 adverse drug reactions (ADRs), including two serious reactions, have been spontaneously reported in the United States in the postmarketing period.

Table 6 (provided by the Applicant) lists the most commonly reported ADRs.

Table 6: Most Frequent Spontaneous ADRs (≥ 2 Reports) in the United States through May 2020 by Preferred Term

MedDRA Preferred Term	Cumulative Data		
	Non-Serious ADRs	Serious ADRs	Total ADRs
Back pain	4	0	4
Myalgia	4	0	4
Anxiety	3	0	3
Arthralgia	3	0	3
Insomnia	3	0	3
Irritability	3	0	3
Nausea	3	0	3
Decreased appetite	2	0	2
Depressed mood	2	0	2
Tremor	2	0	2

Source: Applicant's Safety Update, Table 20, page 37

Serious ADRs of depression and seizure were reported. A serious ADR of depression was reported in a 31-year-old female receiving pitolisant 36.5 mg. The patient had not recovered at the time of the report. A serious ADR of seizure was reported in a male patient (age, dose, and outcome unknown).

Except for tremor, the ADRs listed in Table 6 are included in Section 6 of the Prescribing Information.

Pitolisant is dispensed through specialty pharmacies and patients have periodic follow-up contact with company representatives. Based on a review of solicited adverse drug reactions, the

Applicant identified a potential safety signal for hypersensitivity reactions. The Applicant queried the U.S. safety database to identify all cases in the Immune System Disorders System Organ Class (SOC) and preferred terms commonly associated with hypersensitivity reactions (e.g., throat tightness. The Applicant identified a total of 47 cases. Of these, 10 cases described suspected hypersensitivity reactions. The other reports related to cases of seasonal allergies, environmental allergies, and allergy symptoms such as rhinorrhea and sneezing. The Applicant provided narratives for the 10 cases of suspected hypersensitivity reactions. These cases are summarized in Table 7.

Table 7: Reported Hypersensitivity Reactions, U.S. Postmarketing Database

Event Preferred Terms	Time to Onset	Outcome	Comment
Anaphylactic reaction; drug rash; urticaria	2 months	Positive de-challenge	Dermatologist diagnosed rash as skin fungus; psychiatrist suspected drug reaction to pitolisant
Hypersensitivity; swelling	within 1 month	Positive de-challenge	Included head and neck swelling
Anaphylactic reaction	3 to 4 days	Positive de-challenge	Required epinephrine and steroids
Hypersensitivity, pharyngeal swelling	23 days	Positive de-challenge	Occurred after the administration of baclofen dose; baclofen is a co-suspect medication.
Hypersensitivity	Unspecified	Unknown	
Hypersensitivity	Unspecified	Pitolisant dose decreased, outcome unspecified	
Hypersensitivity	Unspecified	Pitolisant discontinued; outcome unspecified	
Hypersensitivity	Unspecified	Pitolisant discontinued; outcome unspecified	
Hypersensitivity	within 1 month	Pitolisant discontinued; outcome unspecified	
Throat tightness	Unspecified	Pitolisant continued; resolved	

Source: Applicant's Safety Update, Table 22, pages 39–40.

Based on these reports, the Applicant has proposed adding hypersensitivity to Section 6 of the Prescribing Information.

European Postmarketing Data

At the time of the original NDA submission, 135 ADR reports had been submitted in the European countries where pitolisant was authorized. An additional 127 ADR reports have been made since the original NDA review (Appears this way on original

Table 8). The ADRs that comprised ≥ 2% of reports in the postmarketing period—insomnia, headache, nausea, depression, and anxiety—are already listed in Section 6 of the Prescribing Information. Additionally, psychiatric ADRs of nightmare, abnormal dreams, and depression are also included in Section 6.

Table 8: Most Frequently Reported ADRs **(≥2** reports) in the Postmarketing Periods, by Preferred Term, European Data

MedDRA Preferred Term	Original NDA Submission (through 12 February 2019)	Cumulative Data (through 31 March 2020)
	Total ADRs (n=135)	Total ADRs (n=262)
Insomnia	7 (5%)	16 (6%)
Headache	9 (7%)	15 (6%)
Nausea	4 (3%)	12 (5%)
Depression	5 (4%)	8 (3%)
Anxiety	2 (2%)	6 (2%)
Suicidal ideation	3 (2%)	5 (2%)
Hot flush	-	4 (2%)
Abnormal behaviour	4 (3%)	4 (2%)
Somnolence	4 (3%)	4 (2%)
Pruritus	3 (2%)	3 (1%)
Irritability	3 (2%)	3 (1%)
Nightmare	3 (2%)	3 (1%)
Fatigue	3 (2%)	3 (1%)
Myalgia	-	2 (1%)
Peripheral coldness	-	2 (1%)
Abnormal dreams	2 (2%)	2 (1%)
Palpitations	2 (2%)	2 (1%)
Depressive symptom	2 (2%)	2 (1%)
Depressed mood	2 (2%)	2 (1%)

Dyskinesia	2 (2%)	2 (1%)
Tinnitus	2 (2%)	2 (1%)
Weight increased	2 (2%)	2 (1%)
Dizziness	2 (2%)	2 (1%)
Abdominal pain upper	2 (2%)	2 (1%)
Malaise	2 (2%)	2 (1%)

Source: Applicant's Safety Update, Table 25, page

The Serious Individual Case Safety Reports (ICSRs) that have been submitted since review of the original NDA are listed in Table 9.

Suicidal ideation was reported in two of the serious ICSRs. A 48-year-old male patient with narcolepsy and depression experienced suicidal ideation, irritability, restlessness, and belligerence approximately 4 months after starting pitolisant. The patient recovered after pitolisant was discontinued.

A 36-year-old female patient with narcolepsy, Graves' disease, obesity, and eating disorder reported depression and suicidal ideation. The patient reportedly experienced depression and suicidal ideation within a month of started pitolisant and was hospitalized. Pitolisant was discontinued. At the time of the report, the patient was recovering from depression and suicidal ideation.

A reported ICSR of epilepsy is notable given the nonclinical findings and prior reports of epilepsy in the postmarketing period. The serious ICSR of epilepsy concerned a 36-year-old female patient with a prior medical history of epilepsy who experienced increased frequency of seizures after exposure to pitolisant. Pitolisant was discontinued after 2 months of treatment. The outcome of the case is unknown.

A reported ICSR of cardiac arrest in a young (49-year-old) female patient is notable given the reports of sudden death in the OSA development program. The patient has a medical history that was remarkable for narcolepsy, obesity, diabetes, and hypertension. The duration of exposure to pitolisant is not included in the case report. The patient was also prescribed methylphenidate. Both pitolisant and methylphenidate were discontinued. The patient recovered.

Table 9: Listing of the Serious ICSRs Reported in European Postmarketing Databases from 13 February 2019 through 31 March 2020

Case Number	Reaction/Event (PT)	Outcome	Age (years)	Sex	Dose (mg)
FR-BPP-EXT-201900136	Facial paralysis, Motor dysfunction	recovered	31	F	18
FR-BPP-EXT-201900173	Cardiac arrest	recovered	49	F	9
GB-BPP-EXT-201900300	Tension headache	recovered	27	F	18
DE-BPPPROD-201900379	Irritability, Suicidal ideation, Restlessness, Belligerence	recovered	48	M	36
FR-BPPPROD-201900376	Depression, Suicidal ideation	recovering	36	F	27
FR-BPPPROD-201900406	Hyperhidrosis Myalgia	not recovered recovering	48	M	31.5
FR-BPPPROD-201900452	Aggression Behaviour disorder	Unknown recovered	12	M	4.5
FR-BPPPROD-201900476	Epilepsy	unknown	36	F	27

F=female; ICSR= individual case safety report; M=male; PT=preferred term
Source: Adapted from the Applicant's Safety Update, Table 26, Pages 44–45

Reviewer comment: The most commonly reported ADRs are included in the current pitolisant Prescribing Information. The Applicant has identified a signal for hypersensitivity reactions and has included narratives that include potentially life-threatening symptoms (i.e., anaphylaxis, pharyngeal swelling) and positive de-challenge. I agree with the Applicant's proposal to add hypersensitivity to Section 6 of labeling. In addition, hypersensitivity to pitolisant should be a contraindication for use. Two serious reports of seizure and two serious reports of suicidal ideation were submitted in the postmarketing period. Both seizure and suicidal ideation are labeled in the current Prescribing Information. The other serious ICSRs did not reveal a pattern unexpected safety signals. One cardiac arrest (in a patient who recovered) was reported and was notable particularly because of deaths observed in the OSA development program. However, cardiovascular and cardiopulmonary events were otherwise not frequently reported.

4. Conclusion

HARMONY CTP (P11-05), submitted with the original NDA, was a positive, adequate, and well-controlled study for the cataplexy indication. The Agency determined that HARMONY CTP could not stand alone as substantial evidence of effectiveness and that a second study would be required for the cataplexy indication. The Applicant has addressed the deficiencies that prevented HARMONY 1 (P07-03) from serving as a substantiating study. Upon re-review of the data (using the statistical method outlined in the original statistical analysis plan), the Agency found that the positive results did not depend on how missing data were handled. Although the cataplexy subgroup was defined post-hoc and there was no prespecified plan to control for type 1 error for the cataplexy endpoint, the Applicant found that the positive results stood with any clinically-relevant definition of the subgroup and satisfied an extensive list of approaches for controlling type 1 error. The Agency's analysis confirmed these findings.

The safety profile of pitolisant in the postmarketing period has been generally consistent with the safety data presented in the original NDA. The most commonly reported adverse reactions are already represented in labeling. However, the Applicant has identified cases of hypersensitivity that presented with potentially life-threatening symptoms (i.e., anaphylaxis) and that were characterized by a positive de-challenge. Hypersensitivity should be added to Section 6 of the Prescribing Information. In addition, pitolisant should be contraindicated in patients with a known history of hypersensitivity to pitolisant.

Of note, five deaths have occurred in the ongoing OSA development program. Most of the deaths were described as sudden or related to cardiopulmonary failure. The deaths occurred primarily in the uncontrolled, long-term safety extension in a high-risk population, so a clear association with pitolisant exposure has not been established. Cardiovascular and pulmonary adverse reactions were infrequently reported in the postmarketing period, both in the United States and in Europe (where pitolisant has been available since 2016). In patients with narcolepsy, increased heart rate was a commonly reported adverse reaction in the controlled clinical studies and is listed in Section 6 of labeling. Approved labeling also notes that pitolisant increases the QT interval; this effect may be greater in patients with hepatic or renal impairment. No other cardiovascular or pulmonary adverse reactions are included in labeling. The ongoing controlled efficacy and safety study in patients with OSA may provide information about whether there are safety considerations specific to that population (e.g., ECG abnormalities, vital sign changes, or an imbalance of adverse events that could predispose to sudden death. The postmarketing data should also be monitored for sudden deaths and cardiovascular and respiratory adverse reactions.

Overall, the benefit:risk profile of pitolisant in adult patients with narcolepsy and cataplexy is favorable and supports approval of pitolisant for the treatment of cataplexy in adult patients with narcolepsy.

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MARTINE M SOLAGES
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BERNARD A FISCHER
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Supervisory Physician

CLINICAL REVIEW

Application Type	505(b)(1)
Application Number(s)	211150
Priority or Standard	Priority
Submit Date(s)	June 29, 2018 to December 14, 2018 (rolling review)
Received Date(s)	December 14, 2018
PDUFA Goal Date	August 14, 2019
Division/Office	Division of Psychiatry Products/Office of Drug Evaluation I
Reviewer Name(s)	Martine Solages, MD
Review Completion Date	July 7, 2019
Established/Proper Name	Pitolisant
(Proposed) Trade Name	Wakix
Applicant	Bioprojet Pharma/HARMONY Biosciences
Dosage Form(s)	4.45 mg and 17.8 mg film-coated tablets
Applicant Proposed Dosing Regimen(s)	17.8 to 35.6 mg daily
Applicant Proposed Indication(s)/Population(s)	1. Excessive daytime sleepiness (EDS) in adult patients with narcolepsy 2. Cataplexy in adult patients with narcolepsy
Recommendation on Regulatory Action	Approval
Recommended Indication(s)/Population(s) (if applicable)	Treatment of excessive daytime sleepiness in adult patients with narcolepsy.

Table of Contents

Table of Tables

Table of Figures

Glossary

AC	advisory committee
AE	adverse event
AR	adverse reaction
BLA	biologics license application
BPCA	Best Pharmaceuticals for Children Act
BRF	Benefit Risk Framework
CBER	Center for Biologics Evaluation and Research
CDER	Center for Drug Evaluation and Research
CDRH	Center for Devices and Radiological Health
CDTL	Cross-Discipline Team Leader
CFR	Code of Federal Regulations
CMC	chemistry, manufacturing, and controls
COSTART	Coding Symbols for Thesaurus of Adverse Reaction Terms
CRF	case report form
CRO	contract research organization
CRT	clinical review template
CSR	clinical study report
CSS	Controlled Substance Staff
DMC	data monitoring committee
ECG	electrocardiogram
eCTD	electronic common technical document
ETASU	elements to assure safe use
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act of 2007
FDASIA	Food and Drug Administration Safety and Innovation Act
GCP	good clinical practice
GRMP	good review management practice
ICH	International Council for Harmonization
IND	Investigational New Drug Application
ISE	integrated summary of effectiveness
ISS	integrated summary of safety
ITT	intent to treat
MedDRA	Medical Dictionary for Regulatory Activities
mITT	modified intent to treat
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Event
NDA	new drug application

NME	new molecular entity
OCS	Office of Computational Science
OPQ	Office of Pharmaceutical Quality
OSE	Office of Surveillance and Epidemiology
OSI	Office of Scientific Investigation
PBRER	Periodic Benefit-Risk Evaluation Report
PD	pharmacodynamics
PI	prescribing information or package insert
PK	pharmacokinetics
PMC	postmarketing commitment
PMR	postmarketing requirement
PP	per protocol
PPI	patient package insert
PREA	Pediatric Research Equity Act
PRO	patient reported outcome
PSUR	Periodic Safety Update report
REMS	risk evaluation and mitigation strategy
SAE	serious adverse event
SAP	statistical analysis plan
SGE	special government employee
SOC	standard of care
TEAE	treatment emergent adverse event

1. Executive Summary

1.1. Product Introduction

Appears this way on original

Pitolisant is a histamine-3 (H3) receptor antagonist/inverse agonist with a proposed indication of treatment of excessive daytime sleepiness (EDS) in adult patients with narcolepsy and treatment of cataplexy in adult patients with narcolepsy. Of note, narcolepsy is an orphan indication. The proposed dosing regimen includes titration from a starting dose of 8.9 mg (two 4.45 mg tablets) orally once daily during Week 1 to 17.8 mg (one 17.8 mg tablet) orally once daily during Week 2. If needed the dose can be further titrated to 35.6 mg (two 17.8 mg tablets) orally once daily during Week 3. Pitolisant is a new molecular entity that has not previously been approved in the United States. Pitolisant has been authorized by the European Medicines Agency (EMA) and is marketed in Europe under the trade name Wakix. The proposed proprietary name for pitolisant in this application is Wakix.

1.2. Conclusions on the Substantial Evidence of Effectiveness

The Applicant demonstrated a statistically significant effect of pitolisant on EDS in two adequate and well-controlled phase 3 studies in narcolepsy. The primary EDS endpoint, the Epworth Sleepiness Scale (ESS), has been used previously in clinical trials for similar indications. The Division acknowledges the limitations of this endpoint, as it relies on patients to provide hypothetical responses about how they would respond in different situations and is vulnerable to recall bias. Although not pre-specified in the statistical analysis plan, the Maintenance of Wakefulness Test (MWT), a secondary endpoint from the two EDS clinical studies, suggests that pitolisant has a meaningful effect on an objective measure of sleepiness. The Applicant submitted two studies to support an indication for treatment of cataplexy in adult patients with narcolepsy. One study demonstrated pitolisant's efficacy on the primary endpoint of frequency of cataplexy events. The second study included only a subgroup of patients with cataplexy and, while frequency of cataplexy events was a secondary endpoint, this endpoint was not prespecified with a plan to control for the Type-I error rate. The Division considered relying on a single study to grant the cataplexy indication, in part because of the highly statistically significant result of the successful study. However, for a number of reasons (discussed herein), the second indication will not be granted. Pitolisant will therefore be solely indicated for treatment of excessive daytime sleepiness in adults with narcolepsy.

1.3. Benefit-Risk Assessment

Benefit-Risk Integrated Assessment

Pitolisant is a new molecular entity proposed for the treatment of excessive daytime sleepiness (EDS) and cataplexy in adult patients with narcolepsy. Pitolisant was authorized for the treatment of narcolepsy with or without cataplexy by the European Medicines Agency in 2016 but has never been approved for use in the United States.

Narcolepsy is a rare disease and FDA orphan indication that affects 1 in 2000 individuals in the United States. All patients with narcolepsy experience excessive daytime sleepiness and most patients will experience other symptoms including cataplexy, fragmented nighttime sleep, hallucinations during transitions into or out of sleep, and sleep paralysis. Excessive daytime sleepiness may cause patients to fall asleep when they desire to maintain wakefulness, even while talking, working, caring for children, and driving. Cataplexy, an abrupt involuntary loss of muscle tone typically triggered by strong emotions, varies in severity among patients with narcolepsy but is frequently disabling. Patients with narcolepsy are also at higher risk for depression, anxiety, other sleep disorders, excessive weight gain, and accidental injuries. Currently available treatments for excessive daytime sleepiness have limitations that include abuse potential, possible development of tolerance to the wake-promoting effect, and cardiovascular adverse effects. The only other approved treatment for cataplexy, sodium oxybate, carries risks of abuse, respiratory depression, seizure, and central nervous system depression.

The clinical trials that evaluated the effect of pitolisant in patients with narcolepsy were all conducted outside of the United States. The patient population was predominantly white and did not mirror the racial and ethnic diversity of the U.S. population.

Two randomized, double-blind, placebo-controlled trials demonstrated pitolisant's effect on EDS in adult patients with narcolepsy. Although pitolisant is intended for chronic administration, these trials only evaluated its effect over the course of 8 weeks. The development program did not include an assessment of long-term effectiveness. The primary endpoint of both studies was the Epworth Sleepiness Scale (ESS), which was used as the basis of approval for pitolisant. The ESS ranges from a score of 0 (no sleepiness) to 24 (most severe). The difference between pitolisant and placebo was -3.1 points (95% CI -5.73, -0.46) from a baseline score of approximately 18 in both groups in one study and -2.2 points (95% CI -4.17, -0.22; p = 0.03) from a baseline score of approximately 18 in the second study. The Applicant also conducted a responder analysis, defining a response as a score of ≤ 10 at the end of the study or improvement by 3 or more units. Based on this definition, treatment responses in one study were reported in 65% and 35% of patients in the pitolisant and placebo groups, respectively, which corresponds to a

number needed to treat (NNT) of approximately 3 (1/[0.65-0.34). Responder analyses in the second, pivotal study yielded similar results.

In general, ESS scores can be interpreted as follows (Johns 2019):

0 to 5: Lower Normal Daytime Sleepiness
6 to 10: Higher Normal Daytime Sleepiness
11 to 12: Mild Excessive Daytime Sleepiness
13 to 15: Moderate Excessive Daytime Sleepiness
16 to 24: Severe Excessive Daytime Sleepiness

The results suggest that the effect experienced by pitolisant-treated patients (whose baseline ESS scores were approximately 18) was, on average, significant enough to shift EDS from severe to moderate or from moderate to mild.

One randomized, double-blind, placebo-controlled trial demonstrated pitolisant's effect on cataplexy. Another clinical trial examined pitolisant's effects in a subset of patients with cataplexy and found a positive response. Although this analysis was suggestive of an effect in patients with cataplexy, the study was not designed adequately to allow for a conclusive determination.

Based on a moderately-sized safety database of patients with narcolepsy, pitolisant does not appear to cause serious or irreversible harm. There were few serious adverse events in the short-term narcolepsy trials and none occurred in more than one subject. The most common non-serious adverse events in patients with narcolepsy were headache, insomnia, and nausea with risk differences (versus placebo) of 3.7%, 4.1%, and 3.3% respectively. Although some animals exposed to pitolisant developed convulsions, pitolisant use does not appear to correlate with seizure risk in humans. Patients who received pitolisant did not appear to be at higher risk for adverse cardiovascular outcomes or changes in vital signs or electrocardiogram parameters. Laboratory assessments and body weight measurements were comparable in patients receiving pitolisant and patients receiving placebo. While patients treated with pitolisant did not have higher rates of depression (based on adverse event reports and depression screening questionnaires), pitolisant was associated with a higher rate of psychiatric adverse events (e.g., anxiety, hallucinations, irritability) overall. Unlike other approved treatments for narcolepsy, pitolisant does not appear to carry a significant risk of abuse.

At the recommended doses, pitolisant does not prolong the QT interval. However, patients with moderate liver impairment, moderate and

severe kidney impairment, and patients taking medications that affect the metabolism of pitolisant may have higher blood concentrations of pitolisant and a higher risk of QT interval prolongation. Dosage adjustments for these patients are described in product labeling. Pitolisant is contraindicated in patients with severe liver impairment.

Limited data on the impact of pitolisant on pregnancy, neonatal outcomes, and lactation are available.

An open-label, long-term safety study followed patients for up to 5 years. A post-marketing observation study in Europe is ongoing and will follow patients for up to 5 years. The adverse event profiles in these long-term studies and in the postmarketing databases are similar to the adverse event profile observed in the short-term clinical trials. Of note, fewer than 100 patients with narcolepsy have received the highest recommended dose of pitolisant. However, no clear association between dose and development of adverse events is evident from the narcolepsy clinical trials.

Overall, pitolisant's benefit-risk profile is positive. On average, for every three patients treated, one patient can be expected to improve by 3 units on the ESS, e.g., from severe to moderate EDS or from moderate to mild EDS, which is clinically significant. Based on a safety database of 62 patients treated at the to-be-marketed highest dose for 12 months, no harms (i.e., serious adverse events) appeared to be causally related to the drug. Using the rule-of-three, with no drug-related serious adverse events reported in a sample size of 62 patients treated with 35.6 mg pitolisant daily through 12 months, the upper limit of the 95% CI for the risk of a serious adverse event is 1/[62/3) or 5%.

Pitolisant's adverse event profile—particularly the lack of significant cardiovascular effects or abuse potential—offers a safety advantage over other available treatments. In contradistinction to currently approved narcolepsy treatments (stimulant medications, modafinil, armodafinil, and sodium oxybate) pitolisant has shown no potential for abuse and the Agency's Controlled Substances Staff (CSS) did not recommended scheduling to the Drug Enforcement Administration (DEA). Although long-term safety and efficacy data for the highest recommended dose are limited, long-term safety studies and postmarketing data from the last 3 years have not uncovered any unanticipated safety signals in patients receiving pitolisant. I recommend approval of pitolisant for treatment of EDS in adult patients with narcolepsy. Additional studies to characterize the effects of pitolisant on pregnancy and lactation will be required.

At least two adequate and well-controlled studies are generally required to support approval of an indication. In some cases, as noted in guidance for industry (Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products; May 1998) a single study may support approval. One study demonstrated a positive effect of pitolisant on cataplexy; however, it lacked the characteristics that might support

reliance on a single study (i.e., it was small and had no subgroup analyses). Moreover, the study was conducted in Eastern Europe, and ethnicity and race were not reported. Finally, EDS and cataplexy indications are distinct entities such that the data for the EDS indication are not supportive of the cataplexy indication. Thus, with only one adequate and well-controlled study for the cataplexy indication, the data fall short of substantial evidence.

Benefit-Risk Dimensions

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• Narcolepsy is associated with a range of symptoms including excessive daytime sleepiness, cataplexy, hallucinations, nighttime sleep fragmentation, and sleep paralysis. • Individuals with narcolepsy have higher rates of depression, anxiety, excessive weight gain, other sleep disorders, and accidents • Symptoms of narcolepsy are frequently debilitating	EDS and cataplexy associated with narcolepsy can negatively impact an individual's physical health, psychological well-being, and quality of life.
Current Treatment Options	• FDA approved treatments for excessive daytime sleepiness include amphetamines, methylphenidates, modafinil, and armodafinil. These treatments carry risks of abuse and cardiovascular adverse events. Stevens-Johnson Syndrome, a life-threatening dermatologic condition, has been associated with modafinil and armodafinil. • Sodium oxybate is approved for the treatment of both EDS and	Patients with narcolepsy would benefit from additional treatment options, particularly treatments with low human abuse liability potential and limited effects on the cardiovascular system. The only available pharmacologic treatment for patients with cataplexy is highly restricted because of the

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	cataplexy. Risks associated with sodium oxybate include respiratory depression, central nervous system depression, seizure, and abuse. Sodium oxybate is only available through a Risk Evaluation and Mitigation Strategy (REMS) program.	risks of life-threatening adverse events and diversion/abuse.
Benefit	The Applicant conducted two adequate and well-controlled clinical trials to evaluate pitolisant's effect on excessive daytime sleepiness. • HARMONY I (P07-03) and HARMONY I-bis (P09-15) demonstrated a statistically significant effect on the primary endpoint of the Epworth Sleepiness Scale (ESS). In HARMONY I, the least square mean at Week 8 on the ESS was 12.4 for pitolisant and 15.5 for placebo, with a statistically significant treatment difference of -3.1 (95% CI -5.73, -0.46; p = 0.022). More patients in the pitolisant group (45%) met criteria for treatment response (ESS score ≤ 10) than in the placebo group (13%). In HARMONY I-bis, the treatment difference between pitolisant and placebo was -2.2 (95% CI -4.17, -0.22; p = 0.03). Pitolisant-treated patients (65%) were more likely to be responders compared to placebo-treated patients (35%). In HARMONY I, pitolisant also appeared to have a positive effect on the Maintenance of Wakefulness Test (MWT), an objective measure of sleepiness, although the analysis of this endpoint was not prospectively controlled to account for a false positive result. One adequate and well-controlled study evaluated pitolisant's effect on the weekly rate of cataplexy (WRC).	Two adequate and well-controlled clinical trials demonstrated pitolisant's effect on excessive daytime sleepiness. There is substantial evidence to approve pitolisant for the treatment of excessive daytime sleepiness in adult patients with narcolepsy. One adequate and well-controlled study found that pitolisant reduced the frequency of cataplexy events. However, no other clinical trial confirmed this finding. I found that the data are insufficient to support approval for the cataplexy indication, considering: the absence of confirmatory evidence; the fact that this single positive trial did not enroll U.S. patients; the patient population may not have been demographically comparable to the U.S. population (information about race and ethnicity was not collected); and the

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	• HARMONY CTP (P11-05) demonstrated a statistically significant reduction in WRC in the pitolisant group as compared to placebo. • A subgroup analysis of patients with cataplexy in HARMONY I was also suggestive of a positive effect. However, this subgroup analysis was not prospectively controlled to account for a false positive result and did not have an adequate sample size to detect an effect in patients with cataplexy. The findings also depended upon which method was used to handle missing data. • Pitolisant-treated patients had improved scores on the ESS and MWT in HARMONY CTP. However, analyses of these secondary endpoints were not prospectively controlled to account for a false positive result.	likelihood that a trial with U.S. patients would be feasible despite the relatively low prevalence of the disease.
Risk and Risk Management	• Limited data are available regarding long-term safety and efficacy, particularly at the highest recommended dose. Thus far, 62 patients (including 55 patients with narcolepsy) have been exposed to the 35.6 mg dose for at least 12 months in clinical trials. Serious adverse events were uncommon in the development program and did not appear to be drug-related. No irreversible or untreatable non-serious adverse events were identified. Based on the clinical trials safety database, the upper limit of the 95% CI for the risk of a serious adverse event is 5%. Pitolisant has been available for 3.5 years in the European market. Vigibase (the World Health Organization global database of individual case safety reports) has received 121 adverse	Although limited data about the long-term safety and efficacy are available, the open-label, long-term safety study and reports of adverse reactions in the postmarketing period have not identified unexpected safety signals. Additional studies to evaluate the effects on pregnancy and lactation will be required. Product labeling will include recommended dosage adjustments for patients with hepatic and renal impairment and patients taking relevant concomitant medications. Labeling

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	event reports in the postmarketing period. The database has not received any reports of abuse, misuse, withdrawal, dependence or QT interval prolongation. Seizures were not reported as an adverse event in narcolepsy clinical trials but have been reported to the postmarketing databases (2 reports). However, the data are insufficient to conclude that the seizures were drug-related. The most commonly reported adverse events in the postmarketing databases–insomnia (16 reports), headache (15 reports), and nausea (8 reports)–matched the most common adverse events reported in clinical trials. Reports of psychiatric and cardiovascular adverse events appeared consistent with the safety information from clinical trials. • Limited data are available about the effects on pregnancy and lactation. Pitolisant is likely to be used by women of child-bearing potential. • Patients with hepatic and renal impairment and patients taking medications that affect pitolisant metabolism are at increased risk of QT interval prolongation. • Adverse events most frequently associated with pitolisant (compared with placebo) include: headache (18.4% vs. 14.7%), insomnia (5.9% vs. 1.8%), nausea (5.9% vs. 2.6%), upper respiratory tract infection (5.3% vs. 2.6%), musculoskeletal pain (4.6% vs. 2.6%), anxiety (4.6% vs. 1%), increased heart rate/tachycardia (3.3% vs. 0%), hallucinations (3.3% vs. 0%), irritability (3.3% vs. 1.8%), dizziness/light-headedness (3.3% vs. 2.6%), abdominal pain (3.3% vs. 1%), decreased appetite (2.6% vs. 0%), and sleep disturbance (2.6% vs. 1.8%).	will also describe the treatment-emergent adverse events that occurred most frequently in placebo-controlled trials.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	Additional favorable characteristics of pitolisant: • Negligible human abuse liability potential • No association with cardiovascular events or vital sign changes at recommended doses, though pitolisant prolongs the QT interval at higher doses. • No pattern of hyperactivity reactions observed during short-term or long term clinical trials.	

1.4. Patient Experience Data

Patient Experience Data Relevant to this Application (check all that apply)

x	The patient experience data that was submitted as part of the application include:			Section where discussed, if applicable
	x	Clinical outcome assessment (COA) data, such as ESS		[Sec 6.1 Study endpoints, Sec 7.1 Assessment of Efficacy Across Trials, Sec 8.4 Safety Results]
		x	Patient reported outcome (PRO) Daily/Weekly Cataplexy Attacks	
		□	Observer reported outcome (ObsRO)	
		x	Clinician reported outcome (ClinRO) BDI	
		□	Performance outcome (PerfO)	
	□	Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel, etc.)		
	□	Patient-focused drug development or other stakeholder meeting summary reports		[e.g., Sec 2.1 Analysis of Condition]
	□	Observational survey studies designed to capture patient experience data		
	□	Natural history studies		
	□	Patient preference studies (e.g., submitted studies or scientific publications)		
	□	Other: (Please specify)		
□	Patient experience data that were not submitted in the application, but were considered in this review:			
		x	Input informed from participation in meetings with patient stakeholders	
		□	Patient-focused drug development or other stakeholder meeting summary reports	[e.g., Current Treatment Options]
		□	Observational survey studies designed to capture patient experience data	
		□	Other: (Please specify)	
□	Patient experience data was not submitted as part of this application.			

2. Therapeutic Context

2.1. Analysis of Condition

Narcolepsy is a chronic sleep disorder characterized by excessive daytime sleepiness (EDS) that interferes with functioning and is typically accompanied by at least some associated symptoms including cataplexy, sleep paralysis, hypnogogic or hypnopompic hallucinations, and fragmented nighttime sleep. Cataplexy, sudden loss of voluntary muscle tone, can be triggered by strong positive or negative emotions, occurs in most patients with narcolepsy, and is frequently debilitating.

Patients with narcolepsy are classified into two subtypes, primarily based on the presence or absence of hypocretin peptides in the cerebrospinal fluid. Hypocretins, also known as orexins, are neurotransmitters produced in the hypothalamus that modulate wakefulness and REM sleep. Narcolepsy type 1 is thought to be caused by the loss of hypothalamic neurons that produce hypocretin. HLA-DQB1*06:02 is strongly associated with type 1 narcolepsy. In addition to genetic risk factors, post-infectious or autoimmune processes may also play a role, as narcolepsy has been associated with higher anti-streptolysin O (ASO titers) and diagnoses spiked after the 2009 H1N1 influenza pandemic. Cataplexy only occurs in narcolepsy type 1. Narcolepsy type 2 presents with a similar constellation of symptoms but without hypocretin deficiency or cataplexy. The pathophysiology of narcolepsy type 2 is unclear (Scammell, 2015; Division of Sleep Medicine, Harvard Medical School 2018).

According to the International Classification of Sleep Disorders–Third Edition (ICSD3), diagnosis of narcolepsy type 1 requires deficiency of hypocretin-1 in the cerebrospinal fluid (< 110 pg/ml or less than one-third of the normative values with the same standardized assay) or mean sleep latency of < 8 minutes on the Multiple Sleep Latency Test (MSLT), with evidence of sleep-onset rapid eye movement periods (SOREMPs) and cataplexy. A diagnosis of narcolepsy type 2 requires mean sleep latency of < 8 minutes on MSLT and two SOREMPs, in the absence of cataplexy and hypocretin deficiency (Sateia 2014).

Narcolepsy is relatively under-recognized; as many as 50% of affected individuals may not receive a narcolepsy diagnosis. Patients are diagnosed, on average, 5 to 15 years after symptom onset (Thorpy and Krieger 2014). The typical onset of illness occurs in adolescence, but onset can occur at any age. Estimates of prevalence have been limited by low numbers of cases in epidemiologic studies. Available estimates suggest that narcolepsy affects 1 in 2000 individuals in the United States. Prevalence of narcolepsy is higher in males. Prevalence of narcolepsy among white individuals in Europe and North America is similar (approximately 30 cases per 100,000 individuals). Japanese individuals have the highest prevalence of narcolepsy (160 cases per 100,0000 individuals), but the prevalence of narcolepsy in Asian populations overall is similar to the prevalence in white populations. African-Americans also have a high prevalence of narcolepsy (42 cases per 100,000 individuals; Kornum et al 2017).

Patients with narcolepsy are at risk for motor vehicle accidents, falls, and fractures and may have a decreased life expectancy. Narcolepsy is associated with comorbidities such as excessive weight gain, obstructive sleep apnea, depression, nocturnal myoclonus, and sleepwalking and other parasomnias (Kornum et al 2017).

2.2 Analysis of Current Treatment Options

Table 1: Summary of Treatment Armamentarium for Narcolepsy

Medication	FDA Indication	EMA Indication	Target Symptom(s)
Amphetamines Dextroamphetamine Sulfate Mixed amphetamine salts Amphetamine Salts	Narcolepsy, general	No	EDS
Methylphenidate	Narcolepsy, general	Narcolepsy with or without cataplexy in adults when modafinil is ineffective and in children over 6 years	EDS
Modafinil	EDS in narcolepsy, Obstructive Sleep Apnea, shift work disorder	Promote wakefulness in narcolepsy	EDS
Armodafinil	EDS in narcolepsy, Obstructive Sleep Apnea, shift work disorder	No	EDS
Solriamfetol	EDS in narcolepsy and Obstructive Sleep Apnea	No	EDS
Sodium oxybate	Cataplexy or EDS in patients 7 years of age and older with narcolepsy	Narcolepsy with cataplexy	EDS, cataplexy
Pitolisant	No	Narcolepsy with or without cataplexy in adults	EDS, cataplexy

*Sources - Table 1, Medications Approved for Management of Narcolepsy by the FDA and/or EMA, Integrated Summary of Safety, pages 18 to 19; Scammell, 2015

All approved pharmacologic treatments for narcolepsy are controlled substances. Off-label treatments for cataplexy associated with narcolepsy include venlafaxine, fluoxetine, clomipramine, selegiline, and lisdexamfetamine. Non-pharmacologic interventions that are used to manage narcolepsy symptoms include brief regularly scheduled naps, consistent sleep schedule, avoidance of caffeine, alcohol, and heavy meals before bedtime, relaxation before bedtime, regular exercise, and taking safety precautions while driving or operating heavy machinery.

3. Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

Orphan Drug designation was granted to pitolisant in March 2010. In April 2018, Fast Track and Breakthrough Therapy designation were also granted for the cataplexy indication. For the excessive daytime sleepiness indication, Fast Track Designation was granted but Breakthrough Therapy Designation was denied. Rolling review status was granted in June 2018 and the NDA submission was fully received by the Agency in December 2018.

3.2. Summary of Presubmission/Submission Regulatory Activity

In June 2011, the Division of Neurology Products (DNP) provided written responses to the questions submitted by the Applicant regarding primary endpoints, study design, and use of modafinil as an active comparator in the phase 3 studies. DNP noted that the efficacy studies for pitolisant were completed or ongoing at that time and that issues related to the study design would be a matter of review. DNP advised that efficacy for EDS should be supported by positive findings in two adequate and well-controlled studies on both an objective and subjective measure. DNP also indicated that a claim for treatment of cataplexy should be supported by two adequate and well-controlled trials. DNP also noted that an active comparator in the clinical trials was not required.

In May 2015, the Agency provided written responses to questions about the adequacy of clinical trial data for filing of the NDA, stability of the drug product, and other CMC-specific issues. The Agency provided additional guidance regarding nonclinical, biopharmaceutics, clinical pharmacology, abuse liability studies, and the use of foreign data. The Agency noted that the trial data appeared to support the filing of the NDA but that the relatively short duration of treatment in the pivotal efficacy studies for a drug expected to be administered chronically would be an NDA review issue. The Agency advised that: all major human circulating metabolites should be adequately tested in nonclinical studies, comparative dissolution data should be provided in the NDA, the impact of CYP2D6 phenotypes should be addressed in the NDA submission, food effects should be studied, study protocols and primary data from the completed in vitro and preclinical abuse studies and the human physical dependence assessment should be submitted, and abuse-related adverse events from all clinical studies

should be evaluated. The Agency also described requirements for use of foreign data including provision of a rationale that medical care and assessment for narcolepsy is the same in the regions where the studies were conducted and the United States. The Agency referred the applicant to the Final Rule on Foreign Clinical Studies Not Conducted Under and Investigational New Drug Application (http://www.regulations.gov/#!documentDetail;D=FDA-2004-N-0061-0002;oldLink=false) and the guidance on FDA Acceptance of Foreign Clinical Studies Not Conducted Under an IND (https://www.fda.gov/media/83209/download).

DNP and the Applicant held a pre-NDA meeting on September 7, 2016. DNP again noted that the adequacy of the design and the results from the trials to support safe and efficacious use of pitolisant would be review issues. DNP agreed that the clinical and nonclinical trials were appropriate to support filing of the NDA and that the proposed format and content of the Integrated Summaries of Safety and Efficacy appeared adequate. DNP advised that the adequacy of treatment duration in the context of expected chronic drug administration would also be a review issue. The Applicant inquired about the number of patients needed to assess clinical safety (given the orphan indication and difficulties meeting the numbers recommended by the ICH E1 guidance for chronically administered drugs: 300 to 600 patients exposed for 6 months and 100 patients exposed for 1 year). The Applicant noted that the number of participants who received pitolisant in the clinical trials would approach the ICH requirements if clinical trials from all indications were considered. DNP indicated that the extent of exposure including the patients in the non-narcolepsy indications would be adequate to support filing of the NDA. DNP clarified that HARMONY III (open-label, long-term safety study) would not provide robust evidence of efficacy but would provide supportive safety information. DNP suggested the possibility of adding a randomized withdrawal component to HARMONY III to obtain additional efficacy data. DNP advised that the plan for evaluation of the QT/QTc interval and proarrhythmic potential was reasonable, though the adequacy of the studies would again be a matter of review after NDA submission. The need for a risk evaluation and mitigation strategy (REMS) and the need for drug scheduling would also be determined during the review of the NDA. DNP commented that discussions about specific labeling language and about the fact that most of the clinical study data were generated in Caucasians was premature and that available data on race should be submitted with the NDA application. DNP confirmed that this application would be eligible for a Pediatric Research Equity Act (PREA) exemption because of the Orphan Drug Designation. DNP also provided guidance about required drug substance data, stability studies and dissolution data, and product specifications.

In the pre-NDA meeting DNP advised that eligibility for orphan drug exclusivity would be made at the time of marketing approval and if the NDA is approved and no other “same drug” has marketing approval for the same indication, pitolisant would be eligible for orphan drug exclusivity.

Because of Agency realignments, the application was transferred to DPP from DNP in December 2017.

3.3. Foreign Regulatory Actions and Marketing History

Pitolisant was designated as an orphan medicinal product by the European Medicines Agency (EMA) on July 10, 2007 (indication – treatment of narcolepsy). The Applicant received Scientific Advice from the Committee for Medicinal Products for Human Use and the Committee for Orphan Medicinal Products (CHMP and COMP) on September 20, 2007 for the pitolisant development program. The Applicant applied for EMA Marketing Authorization on May 7, 2014 for the indication of treatment of narcolepsy with or without cataplexy. Marketing Authorization was granted on March 31, 2016.

4. Significant Issues from Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety

4.1. Office of Scientific Investigations (OSI)

The Office of Scientific Investigations completed three clinical site inspections. Based on the results of the inspections, the studies appear to have been conducted adequately. The inspections did not raise concerns about data quality or integrity.

4.2. Product Quality

The drug product used in the clinical development program was the same as the to-be-marketed product. The Office of Pharmaceutical Quality (OPQ) reviewed data related to drug substance, drug product, process, facilities, and biopharmaceutics. The OPQ review did not find safety issues that would prevent approval of the application. OPQ found that the excipients are typical of an immediate-release tablet, that the drug substance manufacturing process adequately managed (b) (4) impurities with mutagenic structural alerts, and that the submitted data support the Applicant's proposed 24-month expiry period at room temperature.

4.3. Clinical Microbiology

Not applicable.

4.4. Nonclinical Pharmacology/Toxicology

The nonclinical pharmacology/toxicology review was completed by Dr. James Miller. Please see Dr. Miller's review for full details about the nonclinical data submitted with this application. Key findings from Dr. Miller's review are summarized below.

- Pitolisant demonstrated high binding affinity for native and recombinant human H3 receptors and native mouse brain H3 receptors.

- The main human metabolites (BP1.8054 and BP1.9733) were inactive at the human H3 receptor.

- In rodent studies, pitolisant increased histaminergic neurotransmission. Pitolisant also increased extracellular dopamine, noradrenaline, and acetylcholine in the prefrontal cortex and increased extracellular acetylcholine and t-MeHA levels in the hippocampus. Serotonin turnover was unaffected by pitolisant.

- Pitolisant increased the duration of wakefulness in mice and in cats.

- *In vitro* binding studies demonstrated that pitolisant has high binding affinity for Sigma-1 and Sigma-2 receptors and moderate binding affinity for 5-HT_{2A} and D3 receptors. Pitolisant had low to moderate antagonist activity at 5-HT_{2A} and D3 receptors in a functional binding assay. In other assays, pitolisant was inactive as an antagonist at the 5-HT_{2A} receptor.

- Pitolisant demonstrated hERG channel inhibitory activity in *in vitro* studies, however *in vivo* studies in rats, rabbits, and dogs found no effect on QT intervals and no pro-arrhythmic potential. No arrhythmic events occurred with exposures to high doses in rodents or dogs.

- Pitolisant was found to be non-mutagenic in genetic toxicology studies. No drug-related neoplastic findings were observed after daily oral doses of 30 mg/kg/day in a carcinogenicity study in rats. In mice, no drug-related neoplastic findings were observed up to doses of 75 mg/kg/day.

- In rats, the No Observed Adverse Effect Level (NOAEL) for male and female fertility and early embryonic development is 30 mg/kg/day.

- Convulsions were observed at high doses in rodents. Convulsions may have been due in part to BP1.2526, a major metabolite in the rat; however, pitolisant on its own can produce convulsions without the formation of this metabolite.

- In repeat dose studies in mice, hypoactivity and staggering gait occurred in medium and high dose groups. Convulsions occurred in high dose males. Significant increases in relative liver weights in medium dose and high dose males and females were observed, with correlated centrilobular hypertrophy. Based on the minimal findings at the medium dose, the NOAEL was determined to be 75 mg/kg/day.

- In rats, convulsions occurred in both sexes in the high dose group. The NOAEL was determined to be 30 mg/kg/day.

- In a dose-range-finding study in dogs, convulsions, inability to stand, ataxia, and head swaying were observed at the high dose of 60 mg/kg/day. In monkeys, convulsions occurred at the high dose of 80 mg/kg/day. Increased heart, liver, and adrenal gland weights and

microscopic findings in the gastric mucosa were also noted. In subsequent dosing at the 40 mg/kg/day level, convulsions occurred again and the maximum tolerated dose (MTD) was determined to be 30 mg/kg/day for the monkey. Based on rare occurrence of emesis in repeat dose studies, the NOAEL is considered to be 12 mg/kg/day in monkeys.

4.5. Clinical Pharmacology

The clinical pharmacology review was completed by Dr. Praveen Balimane, PhD in the Office of Clinical Pharmacology. Please see Dr. Balimane's review for full clinical pharmacology information for this application. Key findings from Dr. Balimane's review are summarized below.

- Pitolisant is hypothesized to antagonize H3 receptors, which interrupts the negative feedback loop for histamine release and may stimulate the downstream release of wake promoting neurotransmitters. Pitolisant is also hypothesized to have an inverse agonist effect at the H3 receptor, which stimulates synthesis and presynaptic release of histamine.

- The major circulating metabolites of pitolisant are inactive in humans.

- The mean effective half-life is 20 hours. The mean apparent oral clearance (CL/F) is 43.9 L/hour.

- 90% of pitolisant is excreted in urine, primarily as major metabolites (< 2% unchanged).

- Pitolisant is metabolized primarily by CYP2D6. CYP3A4 and phase 2 glucuronidation play a minor role in metabolism.

- Exposures expected with the highest recommended dose are not associated with clinically significant QT prolongation. However, at exposures that are 2.5-fold what would be expected with the highest recommended dose, the QT interval was prolonged by 9.8 msec (95% CI [7.7, 11.8]). At 4-fold exposures, the QT interval was prolonged by 15.5 msec (95% CI [12, 18.9]).

- Based on the PK changes observed in the hepatic impairment study, a longer dose titration (over 2 weeks (b) (4) and lower dosage cap (17.8 mg (b) (4) are recommended for patients with moderate hepatic impairment. No patients with severe hepatic impairment were included in clinical trials but based on the PK data in moderately-impaired patients, use in severe hepatic impairment is contraindicated.

- Based on the PK changes observed in the renal impairment study, a maximum dose of 17.8 mg per day is recommended in patients with moderate to severe renal impairment. Use is not recommended in end-stage renal disease (ESRD).

- No clinically significant effect on PK was observed in a food effect study.
- Pitolisant exposure increases approximately 2-fold in CYP2D6 poor metabolizers and with co-administration with strong CYP2D6 inhibitors.
- Pitolisant exposures are significantly reduced when co-administered with strong CYP3A4 inducers.
- Co-administration with a CYP3A4 inhibitor had a negligible effect on pitolisant exposures.
- Pitolisant reduces exposures of sensitive CYP3A4 substrates, including oral contraceptives.

4.6. Devices and Companion Diagnostic Issues

This application did not require consideration of any issues related to devices or companion diagnostics.

4.7. Consumer Study Reviews

The Applicant has not submitted any consumer study reviews.

5. Sources of Clinical Data and Review Strategy

5.1. Table of Clinical Studies

The safety review included detailed analysis of the phase 3 narcolepsy studies HARMONY I (P07-03), HARMONY CTP (P11-05), and HARMONY I-bis (P09-15).

Table 2: Principal Safety and Efficacy Studies for EDS Indication

Study Name	Subjects	Description	Dose	Endpoints
HARMONY I* P07-03	Patients ≥ 18y with narcolepsy +/- cataplexy, ESS ≥ 14 110 patients selected; 94 included Patients with cataplexy: 25 in pitolisant group; 27 in modafinil group; 24 in placebo group	Phase 3, randomized, double-blind, placebo and modafinil-controlled trial to assess the safety and efficacy of pitolisant for treatment of EDS in narcolepsy 2-week washout 1-week baseline 3-week titration phase 5-week stable dose phase 1-week withdrawal phase	Starting: placebo OR modafinil 100mg OR pitolisant 10mg Range: modafinil 100mg to 400mg; pitolisant 10mg to 40mg	Primary: ESS Secondary: Frequency and severity of cataplexy attacks MWT SART CGI-C EQ-5D Sleep diary analysis Patient opinion
HARMONY I-bis* P09-15	Patients ≥ 18y with narcolepsy +/- cataplexy, ESS ≥ 14 185 selected; 166 randomized Patients with cataplexy: 50 in pitolisant group; 50 in modafinil group; 26 in placebo group	Phase 3 randomized, double-blind, placebo and modafinil-controlled trial to assess the efficacy and safety of pitolisant in treatment of EDS in narcolepsy 2-week washout 1-week baseline 3-week titration phase 5-week stable dose phase 1-week withdrawal	Starting: placebo OR pitolisant 5mg OR modafinil 100mg Range: pitolisant 5mg to 20mg; modafinil 100mg to 400mg	Primary: ESS Secondary: Daily cataplexy rate MWT SART CGI-C EQ-5D Patient opinion Polysomnography

(b) (4)

5mg pitolisant HCl=4.45mg pitolisant; 20mg pitolisant HCL=17.8mg pitolisant.
ESS – Epworth Sleepiness Scale; MWT – Maintenance of Wakefulness Test; SART – Sustained Attention to Response Task; CGI-C -Clinical Global Impression of Change; EQ-5D – European Quality of Life Questionnaire

Table 3: Principal Safety and Efficacy Studies for the Cataplexy Indication

Study Name	Subjects	Description	Dose	Endpoints
HARMONY CTP* P11-05	Patients ≥ 18y with narcolepsy ≥ 3 cataplexy attacks/week, ESS ≥ 12 117 patients selected; 106 randomized	Phase 3, randomized, double-blind, placebo-controlled trial to assess the efficacy and tolerability of pitolisant in treatment of cataplexy, EDS 1-week washout 2-week baseline 3-week titration phase 4-week stable dose phase 1-week withdrawal phase	Starting: placebo OR pitolisant 5mg Range: pitolisant 5mg to 40mg	Primary: Weekly rate of cataplexy attacks (WRC) during 4-week stable dose period Secondary: WRC during last 2-weeks of treatment WRC > 15 ESS MWT CGI-C EQ-5D Days without hallucinations Z-scores Patient opinion

(b) (4)

5mg pitolisant HCl=4.45mg pitolisant;.20mg pitolisant HCl=17.8mg pitolisant.

Table 4: Phase 3 Supportive Trials for EDS and Cataplexy Indications

Study Name	Subjects	Description	Dose	Endpoints
HARMONY III P09-10	Patients ≥ 18y with narcolepsy ESS ≥ 12 Enrolled in prior studies or use through temporary authorization 104 enrolled 68 completed	Phase 3, open-label study to assess long-term safety of pitolisant in treatment of EDS in narcolepsy 12 months	pitolisant 5mg to 40mg 49/68 completers received 40mg/day for ≥ 9 months	AEs ESS CGI-C EQ-5D Sleep diary analysis Patient opinion <u>Withdrawals</u> AEs – 11 Poor efficacy – 20 Other - 3
HARMONY IV P10-01	Patients ≥ 18y with narcolepsy, +/- cataplexy, stable dose of sodium oxybate, EDS ≥ 12 48 patients	Phase 3 randomized, double-blind, placebo-controlled trial to evaluate the effects of pitolisant as an add on to sodium oxybate on EDS and cataplexy 12 weeks	pitolisant 10mg to 40mg	<u>Primary</u>: ESS <u>Secondary</u>: Average # cataplexy attacks MWT WRC CGI-C EQ-5D Patient opinion

5mg pitolisant HCl=4.45mg pitolisant;.20mg pitolisant HCl=17.8mg pitolisant.
AE – adverse event

Table 5: Phase 2 Narcolepsy Studies

Type of Study	Study Identifier	Main Objective of the Study	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration; Duration of Treatment	Subjects
Efficacy	P05-03	To evaluate the effects of pitolisant on diurnal sleepiness in narcoleptic patients	Single blind, Sequential placebo-controlled	20 mg tablets Dose: 40 mg/day from Day 8 to Day 14 Oral route 14 days	22
Efficacy	P07-07	To evaluate the effects of pitolisant on EDS in patients with narcolepsy and the additive effects in combination with Modafinil (HARMONY II)	Randomized double-blind, parallel group	20 mg tablets Dose: 10 mg or 20 mg or 40 mg per day, placebo, or modafinil 200 mg/day Oral route 8 weeks	14
Uncontrolled	P06-06	Initial tolerability narcolepsy	Open label	20 mg tablets Doses: 10 mg, 20 mg 40 mg/ day Oral route 3 to 9 months	26

Source: Adapted from Sponsor's Tabular Listing of Clinical Studies (Table of Clinical Trials)

5.2. Review Strategy

The safety review included detailed analysis of the phase 3 narcolepsy studies HARMONY I (P07-03), HARMONY CTP (P11-05), and HARMONY I-bis (P09-15). These clinical trials were submitted as evidence of efficacy for the two proposed indications. I also performed a detailed

review of study HARMONY III (P09-10), which is a phase 3, open-label study that provides information about long-term safety. For each of these studies, I reviewed the study reports, adverse event database, laboratory database, electrocardiogram database, vital sign database, and participants' scores on the Beck Depression Inventory. In addition, I reviewed the applicants integrated summary of safety (ISS) database, which includes data from additional narcolepsy trials as well as trials of pitolisant for other conditions, for serious adverse events. I also considered the Applicant's White Paper on (b) (4), the Applicant's draft label, and the most recent Periodic Benefit Risk Evaluation Report. Pitolisant was authorized by the EMA and so post-marketing data from Europe (gathered from the FAERS, Vigibase, and EudraVigilance databases) were also considered in this review, as were the EMA label (summary of product characteristics), and the EMA Public Assessment Report.

The Division consulted the Interdisciplinary Review Team for QT Studies (QT/IRT) for expert review of the Applicant's thorough QT studies. FDA Controlled Substances Staff were also consulted for review of data related to human abuse liability potential. The Division of Pediatric and Maternal Health provided consultation on issues related to use in pregnancy and lactation and provided language for labeling consistent with the Pregnancy and Lactation Labeling Rule (PLLR). The Division of Pharmacovigilance (DPV) in the Office of Surveillance and Epidemiology (OSE) reviewed the European post-marketing data.

The efficacy review centered on HARMONY I, HARMONY CTP, and HARMONY I-bis, all of which were phase 3, randomized, double-blind, placebo-controlled, safety and efficacy trials of pitolisant in adult patients with narcolepsy (b) (4) The Applicant submitted HARMONY I, HARMONY CTP, and HARMONY I-bis as evidence of effectiveness of pitolisant for excessive daytime sleepiness in adult patients with narcolepsy. The Applicant submitted HARMONY CTP and HARMONY I as evidence of effectiveness of pitolisant for cataplexy in adult patients with narcolepsy. The efficacy analysis was conducted primarily by the biometrics reviewer for this application. The efficacy analysis in the EMA Public Assessment Report was also reviewed.

6. Review of Relevant Individual Trials Used to Support Efficacy

6.1. HARMONY I (P07-03)

6.1.1. Study Design

Overview and Objective

The primary objective of this study was to determine the efficacy and safety of pitolisant administered by escalating dose (10 mg, 20 mg, or 40 mg once daily) in patients with narcolepsy and excessive daytime sleepiness (EDS) as compared to placebo and modafinil. Modafinil, the active comparator, is an orally-administered wakefulness-promoting agent that is approved for the treatment of EDS associated with narcolepsy.

Trial Design

HARMONY I (Study P07-03) was a phase 3, randomized, double-blind, placebo- and modafinil-controlled trial to assess the safety and efficacy of pitolisant for the treatment of excessive daytime sleepiness in narcolepsy. This multi-center study was conducted at sites in France, Germany, Hungary, the Netherlands, and Switzerland. While 31 sites were selected, only 24 sites were active.

Patients aged 18 or older who met criteria for narcolepsy based on the International Classification of Sleep Disorders–Second Edition (ICSD-2) and who scored ≥ 14 on the Epworth Sleepiness Scale (ESS) were eligible to be enrolled in the study. The ESS is an 8-question self-report measure that asks patients to rate the likelihood that they would fall asleep while doing daily activities (sitting and reading, watching television, sitting in a public place, riding in a car or on public transport, lying down to rest in the afternoon, sitting and talking to someone, sitting quietly after lunch, and sitting in a stopped car). Items on the ESS are rated from 0 (would never doze) to 3 (high chance of dozing); the maximum score is 24 (Epworth Sleepiness Scale 13.4).

Patients with and without cataplexy were included. Female patients of child-bearing potential were required to use a medically effective method of birth control. Patients with other conditions that could account for EDS were excluded from the trial. Patients with a recent history of substance use disorders were also excluded. Additional exclusion criteria included cardiovascular abnormalities, severe hepatic impairment, psychosis, bipolar disorder, depression, severe anxiety, dementia, seizure disorder, other clinically significant physical illness, previous adverse reaction to central nervous system stimulants, and known hypersensitivity to the study medication or excipients.

At the request of German and Swiss regulatory authorities, patients at sites in those countries were excluded if their Beck Depression Inventory Short Form (BDI-SF) 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. Item G asks specifically about suicidal ideation (Beck and Beck, 1972; Appendix 13.5).

Patients were randomly assigned to either pitolisant, modafinil, or placebo using a predefined list that was developed by an independent individual. Patients and investigators were blinded to the treatment assignment. Pitolisant and placebo were provided as capsules that were identical in appearance and taste and were packaged in identical blister packs. Compliance with treatment was evaluated at each visit by counting the number of capsules remaining in the blister pack and asking patients whether they had taken the investigational treatment as prescribed.

Criteria for withdrawal from the study included voluntary withdrawal of informed consent, loss to follow-up, use of unauthorized treatments, non-compliance or major protocol deviation, and serious adverse events that rendered continued participation unsafe. Participants who were withdrawn from the study were not replaced.

No dietary restrictions were required.

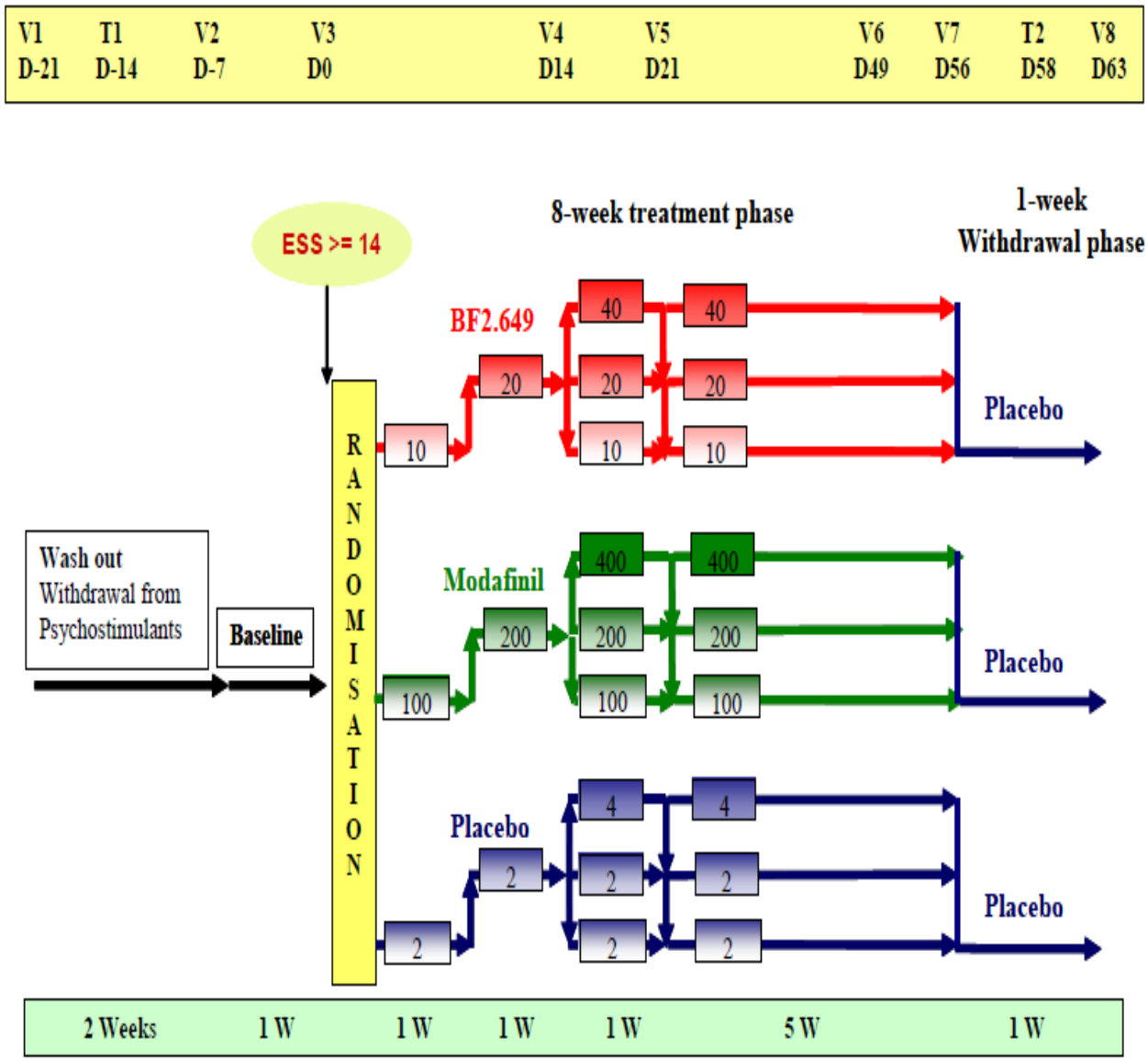
Pitolisant doses in clinical trials were expressed in terms of salt form: 5mg, 10 mg, 20 mg, and 40 mg pitolisant hydrochloride are equivalent to 4.45 mg, 8.9 mg, 17.8 mg, and 35.6 mg pitolisant free base, respectively. Pitolisant doses in HARMONY I ranged from 10 mg to 40 mg once daily (administered orally). The 40-mg dose was chosen as the maximum dose based on prior pharmacodynamic testing of healthy volunteers and patients with narcolepsy.

The study included a 2-week washout period during which patients discontinued stimulants, modafinil, or other treatments for excessive daytime sleepiness. If patients had been taking stable doses of purportedly anti-cataplectic medications (including sodium oxybate, selective serotonin reuptake inhibitors, and serotonin and norepinephrine reuptake inhibitors) for at least one month prior to the trial, they could continue taking their current dose during the trial.

After the 1-week screening period, eligible patients were randomized 1:1:1 to receive either pitolisant (starting dose of 10 mg), modafinil (starting dose of 100 mg), or placebo for 1 week. The following week, patients were titrated to the medium dose (20 mg of pitolisant or 200 mg of modafinil). The following week (Day 14), doses could be adjusted by the investigators to improve efficacy and tolerability. Patients who had not improved sufficiently but who were tolerating the study medication could be increased to the high dose (40 mg of pitolisant or 400 mg of modafinil), patients who had improved sufficiently and were tolerating the study medication were continued on the medium dose, and patients who had difficulties tolerating the study medication were tapered down to the low dose (10 mg of pitolisant or 100 of modafinil). Patients in the placebo group underwent mock dose titrations. On Day 21, doses could be reduced at the discretion of the investigator; no dose increases were permitted. Patients remained on this final dose for the duration of the 5-week treatment phase. During a 1-week withdrawal phase, patients in all groups received placebo.

The schematic (provided by the Sponsor) in the following figure summarizes the study design (Figure 1).

Figure 1: Study Design - HARMONY I (P07-03)



Source- Harmony I (P07-03), Clinical Study Report, page 24

Study Endpoints

The primary endpoint in HARMONY I was the ESS. The Applicant has concluded that the ESS is well-validated and both sensitive and specific for detecting excessive daytime sleepiness and therefore suitable as a primary endpoint.

No other primary or key secondary endpoints were pre-specified with a plan to control for Type-I error, although the Applicant notes in their Integrated Summary of Efficacy that the

frequency and severity of cataplexy attacks was assessed as a "second primary endpoint" in patients with cataplexy. Patients completed sleep diaries that were used to collect information about the frequency and duration of episodes of daytime sleepiness, the frequency and severity of cataplexy attacks, frequency and duration of nocturnal awakenings, frequency of hallucinations, and incidence of sleep paralysis. The Maintenance of Wakefulness Test (MWT), which measures a patients' ability to remain awake under conditions that promote sleep (i.e., while reclining in a quiet and dimly lit room), was also a secondary endpoint in this study. The MWT measures sleep latency–the time it takes for a patient to fall asleep under sleep-promoting conditions. The protocol also included another objective measure, the Sustained Attention to Response Task (SART). The SART presents patients 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 measures vigilance and attention, which may be impacted by EDS. Additional secondary endpoints included the Clinical Global Impression of Change (CGI-C), the response rate (defined as proportion of patients with ESS score ≥ 10 at the end of treatment), the European Quality of Life Questionnaire (EQ-5D), and patient's global opinion on the effect of the drug. Evaluation of safety included adverse event recordings, vital signs, physical examinations, laboratory evaluations, electrocardiograms, the Beck Depression Inventory (BDI), and assessment of withdrawal symptoms.

Table 6 (provided by the Sponsor) summarizes the schedule of assessment activities in the study. Physical examination, electrocardiogram, laboratory assessments, and MWT were conducted at baseline and at the end of the study. ESS was administered at each study visit. Patients' sleep diaries were reviewed throughout the study. Adverse event records were reviewed at each study visit. The BDI-SF was performed at each visit for participants at German and Swiss sites; the protocols in other participating studies did not require this measure.

Reviewer comment: Clinical trials for this development program were underway when the Applicant sought guidance from the Agency. The Agency does have reservations about use of the ESS, as it requires patients to answer hypothetical questions and is also subject to recall bias. However, the ESS is widely-used in the narcolepsy population and has been used previously to support approval of narcolepsy treatments. Although not prespecified as a key secondary endpoint, the MWT and SART provide additional objective efficacy data.

Table 6: Schedule of Assessments - HARMONY I (P07-03)

Visit	Screening (VI)	Phone Contact	Baseline (V2)	Inclusion (V3)	Titration (V4)	Titration (V5)	Control (V6)	Endpoint (V7)	Phone Contact	Withdraw (V8)	Premature dropout
Study day	D-21	D-14+1	D-7+2	D0+2	D14±2	D21±2	D49±2	D56±2	D58±1	D63±2	+3
Informed Consent	X		X (de novo)								
Narcolepsy history	X		X (de novo)								
Physical exam, ECG, lab tests	X		X (de novo)					X			X
Vital signs	X		X	X	X	X	X	X		X	X
BDI and/or suicidal item G	X		X	X	X	X	X	X		X	X
Inclusion/exclusion criteria	X		X (de novo)	X							
Randomization				X							
ESS	X		X	X	X	X	X	X		X	X
CGI EDS + CGI Cataplexy			X	X	X	X	X	X		X	X
SART				X				X			X
40-minute MWT				X				X			X
EQ-5D			X	X		X		X		X	X
Adverse events		X	X	X	X	X	X	X	X	X	X
Delivery of sleep diary			X								
Review of sleep diary				X	X	X		X		X	X
Administration of drugs				X	X	X	X	X			
Drug accountability					X	X	X	X		X	X
Withdrawal symptoms									X	X	X
Patient's global opinion					X	X	X	X	X	X	X

1 The 3-week escalating dosage phase is followed by a 5-week stable-dose period during which dose will be 10, 20 or 40 mg/d for BF2.649; 100, 200 or 400 mg/d for Modafinil or placebo.
2 Complete biological examination including: NFS, platelets, urea, prothrombin ratio or factor V creatinine, SGOT, SGPT, GGT, alkaline phosphatases, bilirubin, glycemia, ionogram and serum pregnancy test for woman of childbearing potential.
3 Measurement of ESS at baseline (at D-7 and at D0) and at endpoint (at D49 and at D56) will be repeated 2 times after an interval of 1 week during a visit.
4 At each visit, the patient shall bring back his treatment together with his sleep diary
5 The premature withdrawal of study visit should be conducted a maximum of 3 days after the last dose of study drug.
6 The window for V2 and V3 is + 2 days, that for V4, V5, V6, V7 and V8 is ± 2 days; that for V9 is ± 3 days
7 De novo patients could be recruited by directly entering V2. All inclusion and exclusion criteria should be examined during V2.
8 The item should be performed only in do novo patients

Source: Protocol, HARMONY I (P07-03), Table 3, Overall Time and Events Schedule, page 35

Statistical Analysis Plan

Clinical trials for this NDA were conducted entirely in Europe without prior guidance from the FDA. Therefore, the Applicant and the FDA had not reached agreement on the statistical plan before it was finalized. Semhar Ogbagaber, Ph.D. conducted the statistical review of the NDA application. For a detailed evaluation of the SAP, please refer to Dr. Ogbagaber's review.

Study populations: The Applicant included all randomized patients who received at least one dose of the drug in their modified intention to treat population. All randomized patients, regardless of whether they received treatment, were included in the extended Intent-to-Treat population. Patients who remained in the study until at least V6 without major protocol violations were included in the Per-protocol population.

Comparison tests: The type I error rate was set at a nominal error rate of 5%. Two-sided confidence intervals were imputed.

Missing data: Estimation for missing values were made by carrying forward the arithmetic mean of the last 2 values. For patients who did not have any post-baseline values, the final value was assimilated with baseline.

Statistical Methodology for the Primary Efficacy Analysis: In the primary efficacy analysis, the Applicant used a linear mixed effect model to compare the differences between the final Epworth Sleepiness Scale results in the treatment groups. Statistical significance was defined as $p < 0.05$.

Statistical Methodology for Secondary Analyses: The statistical analysis plan did not include a plan to prospectively assess secondary endpoints with control of the Type-I error rate. The ESS responder rate was evaluated using logistic regression and the number of cataplexy attacks was analyzed using a Poisson regression. The statistical analysis plan indicated that the MWT and SART results would be analyzed with a non-parametric Mann-Whitney test, however a pooled t-test was used in the Sponsors' final data analysis. The Applicant did conduct the Mann-Whitney test analysis in response to a request from the biometrics reviewer.

Protocol Amendments

In addition to correction of typographical errors and edits made for clarity, substantive amendments to the study protocol included the addition of the BDI-SF at the request of German authorities, a change in the age limits for inclusion to allow patients 18 and older to participate (the prior version of the protocol allowed inclusion of patients 18 to 65), and an extension of the enrollment period by 5 months.

6.1.2. Study Results

Compliance with Good Clinical Practices

The Applicant has provided attestation that HARMONY I was conducted in accordance with Good Clinical Practice (GCP).

Financial Disclosure

The Applicant has adequately disclosed financial interests and arrangements with clinical investigators. The Applicant did not disclose any interests or arrangements that raised

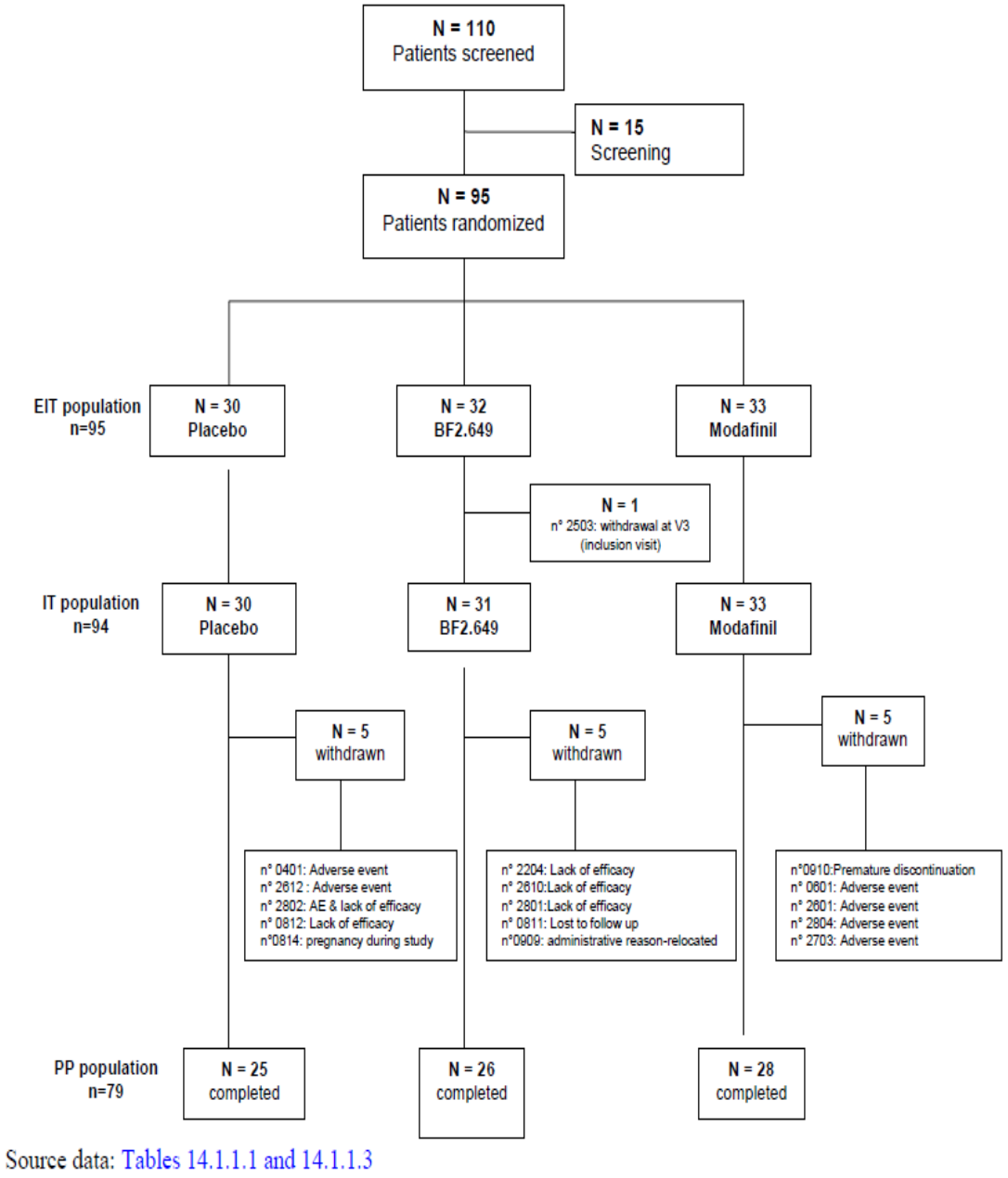
questions about the integrity of the study data.

Patient Disposition

95 patients were randomized: 32 to pitolisant, 30 to placebo, and 33 to modafinil (Figure 2). One patient who was randomized to the pitolisant group was excluded from the Applicant's intention to treat analysis because he did not take the study treatment and did not attend visits after randomization. Of the 94 remaining randomized patients, approximately 84% of patients in all three treatment groups completed the study (26 in the pitolisant group, 25 in the placebo group, and 28 in the modafinil group).

In the placebo group, two patients withdrew from the study because of adverse events, one patient withdrew secondary to both adverse events and lack of efficacy, one patient withdrew because of lack of efficacy, and one patient withdrew because of pregnancy. In the pitolisant group, three patients withdrew because of lack of efficacy, one patient was lost to follow-up, and another patient left the study for administrative reasons (relocated to another geographic area).

Figure 2: Disposition of Patients - HARMONY I (P07-03)



Source – Clinical Study Report, Harmony I (P07-03), page 53

Protocol Violations/Deviations

The Applicant reported two major protocol deviations in HARMONY I. The ESS score was not available after Visit 3 for one patient and after Visit 6 for another patient. Both patients prematurely withdrew from the trial.

Table of Demographic Characteristics

The patient population in all treatment groups was overwhelmingly White/Caucasian. Mean age in the placebo group was 6 years greater than that in the pitolisant group; the age range in the placebo group was also wider, with a maximum age of 75 years in the placebo group compared with 65 years in the pitolisant group. Patients in the placebo group were more likely to be female (Table 7). Most study participants were in France, Germany, or Hungary (Figure 3).

Table 7: Demographic Characteristics of HARMONY I (P07-03)

Demographic Parameters	Pitolisant (N= 31)	Placebo (N = 30)	Modafinil (N = 33)
Sex			
Male (%)	20 (64.5%)	13 (43.3%)	18 (54.5%)
Female (%)	11 (35.5%%)	17 (56.7%)	15 (45.5%)
Age			
Mean years (SD)	35.7 (14.6)	41.3 (14.8)	39.2 (14.6)
Median (years)	33	39.5	40
Min, max (years)	19, 65	19, 75	18, 65
Race			
White (%)	29 (93.5%)	28 (93.3%)	32 (97%)
Black or African American (%)	2 (6.5%)	2 (6.7%)	1 (3%)
Asian (%)	0 (0%)	0 (0%)	0 (0%)
American Indian or Alaska Native (%)	0 (0%)	0 (0%)	0 (0%)
Native Hawaiian or Other Pacific Islander (%)	0 (0%)	0 (0%)	0 (0%)
Not Collected (%)	0 (0%)	0 (0%)	0 (0%)

Reviewer Comment: The difference in age in the pitolisant and placebo groups could theoretically have impacted results if older patients were more susceptible to adverse events or less likely to respond. However, given that the groups were comparable in terms of severity of narcolepsy symptoms and co-morbid medical conditions, the age difference observed in this study is unlikely to have had a significant effect. Patients in the placebo group were more likely to be female. However, no pathophysiologic or mechanistic reason to suspect significant gender effects has been identified. The pharmacokinetics of pitolisant are not impacted by age or gender.

HARMONY I was conducted entirely in Europe and the study population does not reflect the demographic profile of the U.S. population. The Applicant has submitted a White Paper on the

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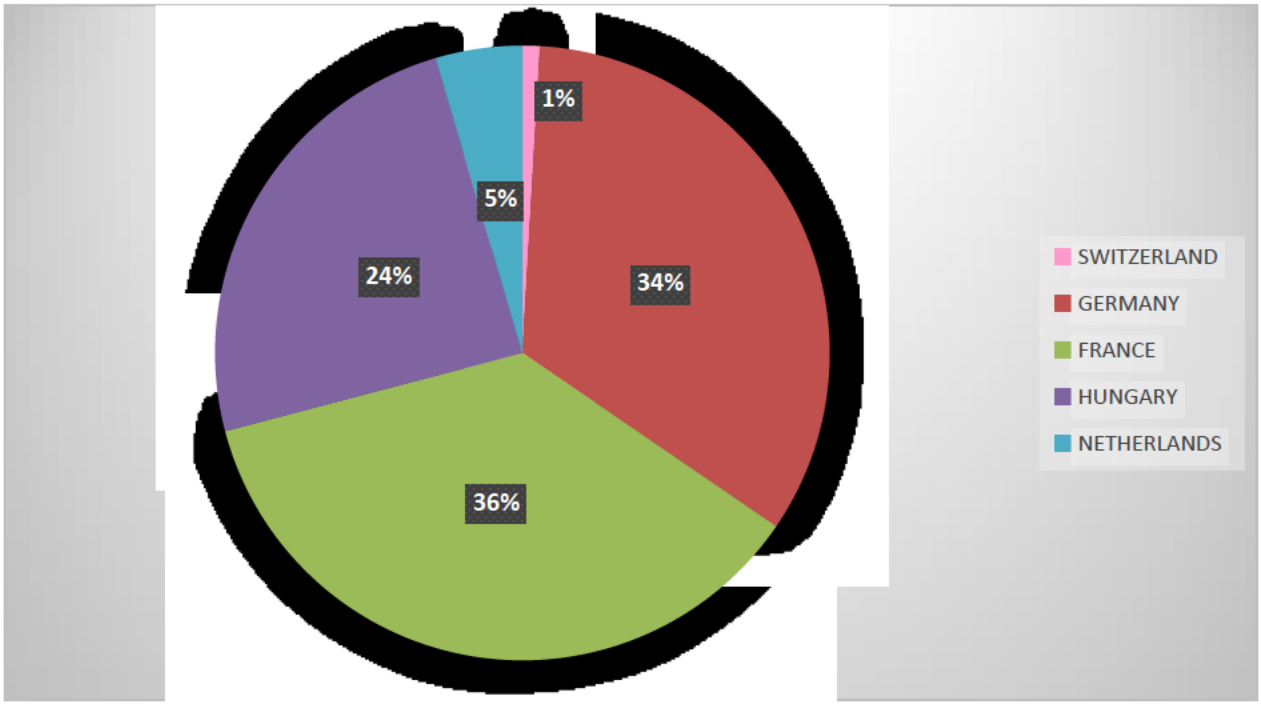
Figure 3: Study Participants by Country – HARMONY I (P07-03)



Other Baseline Characteristics (e.g., disease characteristics, important concomitant drugs)

The pitolisant and placebo groups did not differ significantly in terms of disease characteristics and use of concomitant medications (**Table 9** and **Table 10**). Approximately 80% of patients in each treatment group (25 patients in the pitolisant group, 27 patients in the modafinil group, and 24 patients in the placebo group) were identified as having narcolepsy associated with cataplexy. The baseline ESS score was 17.8 in the pitolisant group, 18.9 in the placebo group, and 18.5 in the modafinil group. The average duration of narcolepsy was 11.1 years in the pitolisant group, 15.2 years in the placebo group, and 12.2 years in the modafinil group. A similar proportion of patients in all treatment groups were concomitantly prescribed SSRIs and other antidepressants. No patients in the pitolisant or placebo groups reported a prior diagnosis of depression. One patient in the pitolisant group reported a diagnosis of anxiety. One patient in both the pitolisant and placebo groups reported a prior history of obstructive sleep apnea.

Table 9: Baseline Disease Characteristics - HARMONY I (P07-03)

	PLACEBO (N=30)		BF2.649 (N=31)		MODAFINIL (N=33)		p-value[2]
Parameter	**N**	**Value[1]**	**N**	**Value[1]**	**N**	**Value[1]**	
Duration of Narcolepsy (yrs)	30	15.2 [9.2; 25.3]	31	11.1 [8.2; 18.0]	33	12.2 [5.7; 20.3]	0.459
Multiple Sleep Latency Test (min)	18	5.4 ± 2	20	3.7 ± 2.6	20	4.9 ± 2.4	0.080
History of Drug Abuse or Dependence Disorder	30	0.0 (0)	31	0.0 (0)	33	0.0 (0)	.
History of Cataplexy		80.0 (24)		80.6 (25)		81.8 (27)	1.000
History of Associated Symptoms							
Sleep paralysis		50.0 (15)		48.4 (15)		66.7 (22)	0.282
Hallucinations		63.3 (19)		58.1 (18)		63.6 (21)	0.896
Automatic behavior		30.0 (9)		48.4 (15)		48.5 (16)	0.259
Dyssomnia		46.7 (14)		58.1 (18)		60.6 (20)	0.551
Baseline ESS (V2 + V3)/2	30	18.9 ± 2.5	31	17.8 ± 2.5	33	18.5 ± 2.7	0.246
Baseline CGIS (Scale 1=EDS)	30	5.3 ± 0.8	31	5.2 ± 0.9	33	5.2 ± 1.2	0.903
Baseline CGIS (Scale 2=cataplexy)	30	3.1 ± 1.9	31	3.6 ± 1.7	33	3.0 ± 1.9	0.440
Baseline EQ-5D	29	64 ± 19.2	31	65.3 ± 21.3	32	58.7 ± 19.4	0.390
Baseline SART-NOGO	30	8.0	30	9.1	33	9.0	0.692
Baseline SART-GO	30	3.5	30	3.6	33	3.3	0.808
Baseline SART-TOTAL	30	11.4	30	12.5	33	11.4	0.995
Baseline MWT	30	8.4	31	7.4	33	8.8	0.639

1 Data are expressed as Mean ± SD except for narcolepsy characteristics (expressed as % (n)), duration of narcolepsy
(expressed as Median [25th%; 75th%]) and MWT, SART (Geometric Mean)
2 Details on the statistical tests used to compare groups are provided in section 9.7.1.
Source: HARMONY I Clinical Study Report, Table 7, Summary of Baseline Narcolepsy Characteristics – IT Population, page 57

Table 10: Patients Receiving Concomitant Medications - HARMONY I (P07-03)

Treatment Group	N	%
Pitolisant	21	67.7%
Modafinil	25	75.6%
Placebo	20	66.7%

Purported anti-cataplectic effect was the given indication for all antidepressants prescribed to pitolisant-treated and placebo-treated patients. Two patients in the pitolisant group and one patient in the placebo group were prescribed sodium oxybate for anti-cataplectic effect (Table 11). The protocol permitted patients to remain on anti-cataplectic medications if patients had been on stable doses for at least 1 month prior to enrolling in the trial.

Table 11: Concomitant Medications - HARMONY I (P07-03)

Concomitant Medication (Class)	Pitolisant	Modafinil	Placebo
OTHER ANTIDEPRESSANTS[1]	22.6%	18.1%	13.3%
PROPRIONIC ACID DERIVATIVES[2]	22.6%	6%	10%
ANILIDES[3]	16.1%	21.2%	13.3%
GLUCOCORTICOIDS	12.9%	3%	3.3%
SELECTIVE SEROTONIN REUPTAKE INHIBITORS (SSRIs)[4]	12.9%	15.1%	16.7%
ACE INHIBITORS, PLAIN	9.8%	9%	3.3%
OTHER ANTIHISTAMINES FOR SYSTEMIC USE	9.8%	0	0
PROGESTOGENS AND ESTROGENS, FIXED COMBINATIONS	9.8%	0	3.3%
BETA BLOCKING AGENTS, SELECTIVE	6.5%	18.1%	6.7%
FLUOROQUINOLONES	6.5%	0	3.3%
OTHER PSYCHOSTIMULANTS AND NOOTROPICS[5]	6.5%	6%	13.3%
PROTON PUMP INHIBITORS	6.5%	18.1%	10%
PLATELET AGGREGATION INHIBITORS EXCL. HEPARIN[6]	0	30.3%	13.3%

1. Other antidepressants - duloxetine, reboxetine, venlafaxine
2. Propionic acid derivatives - flurbiprofen, ibuprofen
3. Anilides – acetaminophen, thomapyrin
4. SSRIs - citalopram, escitalopram, fluoxetine, paroxetine
5. Other psychostimulants and nootropics - piracetam, sodium oxybate
6. Platelet aggregation inhibitors excluding heparin -acetylsalicylic acid, clopidogrel

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

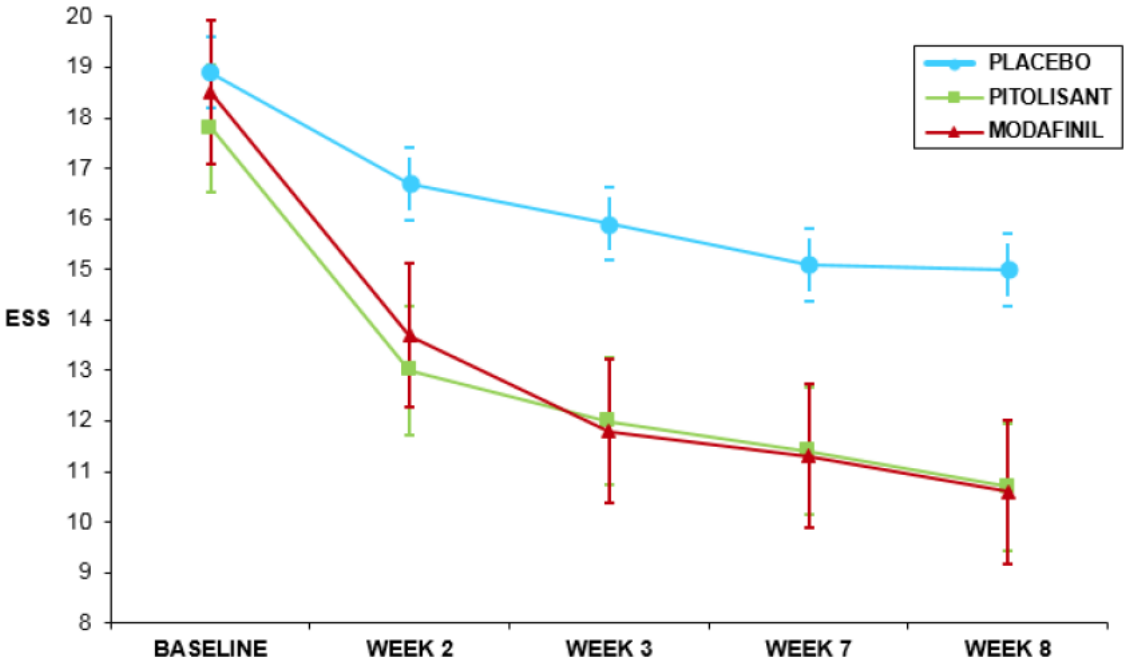
More than 90% patients in each treatment group met the Applicant's definition of good compliance to treatment (compliance index of ≥ 80%).

Efficacy Results – Primary Endpoint

The Applicant's analysis of the primary efficacy endpoint found that the least square mean at Week 8 on the ESS was 12.39 in the pitolisant group and 15.48 in the placebo group, with a statistically significant treatment difference of -3.10 ($p = 0.022$, Figure 4).

The Applicant performed a sensitivity analysis in the per-protocol population and found similar results. No significant difference between pitolisant and modafinil was observed in the Applicant's non-inferiority analysis. FDA analysis of the primary endpoint resulted in similar results. The FDA statistical review also confirmed the Applicant's findings using an alternate analysis using mixed model repeated measures (Table 12). Please see the biometrics review for full details of the FDA analysis.

Figure 4: ESS Score (Mean ± Standard Error of the Mean) from Baseline to Week 8 (ITT Population) – HARMONY I (P07-03)



Source – Clinical Study Report, HARMONY I (P07-03), Figure 4, page 60

Table 12: Adjusted Change from Baseline to Week 8 in ESS Total Score - HARMONY I (ITT; MMRM)

Visit	Placebo N=30	Pitolisant N=31	Modafinil N=33	Pitolisant v. Modafinil
Baseline (BL)*				
N	30	31	33	
Mean ± SD	18.9 ±2.5	17.8 ±2.5	17.8 ±2.5	
Change at Week 8				
N	25	26	28	
LS Mean ± SE	-2.73±0.90	-6.41 ±0.88	-7.09 ±0.86	
p-value		0.002	0.0002	0.55
LS mean differences ± SE		-3.68±1.16	-4.36±1.14	0.68 ±1.14
95% CI for differences		(-5.96, -1.39)	(-6.59, -2.12)	(-1.56, 2.92)

MMRM – Mixed Model Repeated Measures
Source – Biometrics review, Table 15

Data Quality and Integrity

Data for HARMONY I were submitted in electronic common technical document format (eCTD). The data were organized sufficiently well to allow for review. No sites were excluded from analysis because of suspicion of fraud. The Applicant has attested that no investigators received significant financial compensation. Study monitoring was performed by (b) (4) a Clinical Research Organization (formerly known as (b) (4)).

Efficacy Results – Secondary and other relevant endpoints

The objective secondary endpoints included in the study were the number of cataplexy attacks, MWT, and SART. Of note, no prospective plan to assess the endpoints with control of the Type-I error rate was included in the statistical analysis plan.

Daily Rates of Cataplexy: In the subgroup of patients with cataplexy, the Applicant found that pitolisant-treated patients had significantly fewer daily cataplectic events ($p = 0.034$) when participants with zero or missing cataplectic events were imputed. Patients in the pitolisant group had a mean baseline daily cataplexy rate of 0.5 events/day; at the end of treatment the daily cataplexy rate was 0.2 events/day. Patients in the placebo group had a daily cataplexy rate of 0.4 events/day at baseline and at the end of treatment.

The biometric review notes that when subjects with zero or missing cataplectic events were ignored, pitolisant did not demonstrate a statistically significant improvement in daily rates of cataplexy over placebo.

MWT and SART: The Applicant found that pitolisant-treated patients demonstrated increased sleep latency on the MWT as compared to patients in the placebo group (Table 13, $p = 0.044$). Sleep latency increased more in the modafinil group than in the pitolisant group, but the difference was not statistically significant ($p = 0.173$). Error rates on the SART were comparable in the pitolisant and placebo groups at baseline but significantly lower ($p = 0.041$) in the pitolisant group as compared to placebo after treatment. At the request of the biometrics reviewer, the Applicant conducted additional analyses using the Mann-Whitney test (with and without imputation of the last observed value); the results of these analysis were consistent with the original findings.

Table 13: MWT and SART Results - HARMONY I (P07-03)

	IT (N=94)					
	Comparison	Control	BF	Est.	95% CI	P
MWT	BF/PL	7.6	9.7	1.47	[1.01 ; 2.14]	0.044
	BF/MD	15.1	9.7	0.77	[0.52 ; 1.13]	0.173
SART-GO	BF/PL	2.7	2.2	0.80	[0.57 ; 1.13]	0.202
	BF/MD	2.5	2.2	0.81	[0.56 ; 1.15]	0.233
SART-NOGO	BF/PL	8.1	7.5	0.82	[0.67 ; 0.99]	0.042
	BF/MD	7.1	7.5	1.03	[0.83 ; 1.28]	0.780
SART-TOTAL	BF/PL	10.3	8.9	0.79	[0.64 ; 0.99]	0.041
	BF/MD	9.1	8.9	0.90	[0.70 ; 1.14]	0.363

*MWT – Maintenance of Wakefulness Test; SART-GO – sum of the number of times button participant failed to press button when appropriate; SART-NOGO – sum of number of times participant pressed button inappropriately; SART-TOTAL – sum of SART-NOGO and SART-GO; BF – pitolisant; PL – placebo; MD – modafinil
Source – Applicant's Integrated Summary of Efficacy, Table 16, page 65

CGI-C: Scores on the CGI-C questionnaire for EDS improved in all treatment groups by Visit 7. However, the difference between scores in pitolisant-treated and placebo-treated patients did not reach statistical significance (p = 0.051). Similarly, the Applicant did not find a significant difference in scores on the CGI-C questionnaire for cataplexy on Visit 7 (p = 0.380).

ESS ≤ 10: The Applicant defined response as a final ESS score of ≤ 10. The Applicant calculated a responder rate and found that more patients in the pitolisant group (45%) responded than in the placebo group (13%; p = 0.013). No difference in response rate between the pitolisant and modafinil group was observed.

EQ-5D: The Applicant assessed quality of life using the EQ-5D, which is a self-report measure that asks patients to rate effects on mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Answer choices for each domain range from level 1 (no impairment) to level 5 (severe impairment). The EQ-5D also includes a visual analogue scale that asks patients to rate their overall health on a scale of 0 to 100. EQ-5D-5L scores are converted to index values that can be compared to country-specific value sets. No statistically significant change in quality of life scores in the treatment groups was found.

Patient Global Opinion on Treatment: The Applicant assessed patients' global opinion on the effect of treatment using a 6-level scale. Patients were asked to report whether they had experienced marked effect, moderate effect, minimal effect, no change, minimal worsening, or substantial worsening. At Visit 7, patient's global opinion on the effect of treatment improved for 80% of patients in the pitolisant group compared with 56% of patients in the placebo group (p = 0.034). No significant difference in patient global opinion was observed between the pitolisant and modafinil groups.

Reviewer comment: Pitolisant-treated patients experienced a significant effect on two objective measures, the MWT and the SART. Measures assessing the clinical meaningfulness and quality of life were generally not significant, though patients in the pitolisant group were more likely to report that they had benefited from treatment.

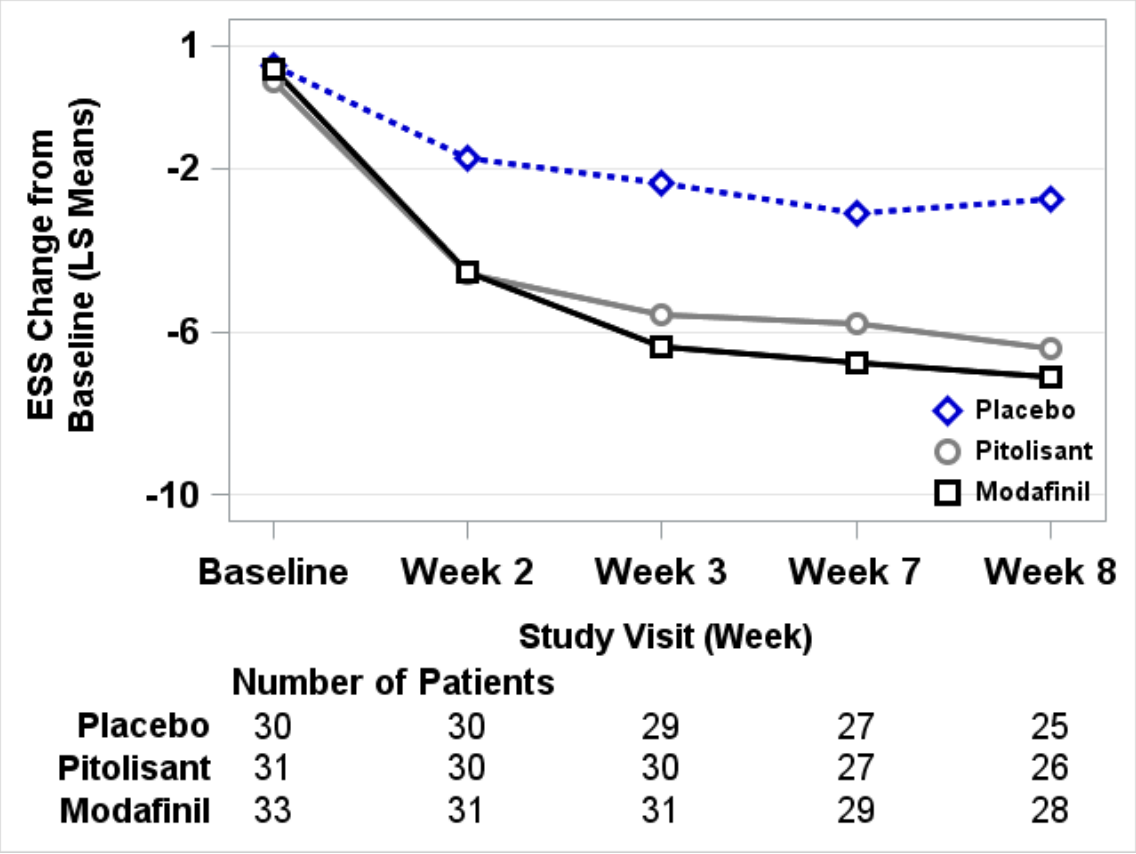
Dose/Dose Response

The data from this single trial did not provide definitive data about dose/dose response. Please see Section 7.1.4 for full discussion of dose-response.

Durability of Response

This study compared ESS scores at baseline and at the end of treatment and did not assess the durability of response. However, a separation between pitolisant and placebo was observed as early as Week 2 (Figure 5).

Figure 5: Change in ESS Total Score by Visit - HARMONY I (ITT)



Source – Biometrics Review, Figure 8

Persistence of Effect

This trial did not assess the persistence of effect after treatment was discontinued.

Additional Analyses Conducted on the Individual Trial

The biometrics reviewer conducted a re-analysis of the primary efficacy data that confirmed the finding of a significant mean difference between pitolisant and placebo on the primary endpoint. The description of the analysis (excerpted from the biometrics review) is as follows:

"*Re-analysis of primary efficacy data using median shift of Hodges-Lehmann and permutation test (non-parametric methods) resulted in consistent results with Applicant's conclusion. Hodges-Lehmann utilizes the median of all pairwise differences between treatment groups."*

Table 14: Hodges-Lehmann median shift and 95% CI on final ESS value (HARMONY 1)

	Pitolisant vs. Placebo	Modafinil vs. Pitolisant
Estimate (95% CI)	4 (0.5, 7)	0.5 (-3.5, 3.5)
p-value*	0.02	0.78

Source: Biometrics Review, Table 19

*The p-value is extracted from Wilcoxon rank test.

"The p-value from the permutation test (a total of 1000 permutations) showed significant mean differences between pitolisant and placebo (p = 0.01) and non-significant mean ESS scores between pitosilant and modafinil (p = 0.906)."

6.2. HARMONY CTP (P11-05)

6.2.1. Study Design

Overview and Objective

HARMONY CTP (P11-05) was a phase 3, randomized, double-blind, placebo-controlled trial to assess the safety and efficacy of pitolisant for the treatment of cataplexy attacks and excessive daytime sleepiness in narcolepsy. This multi-center study was conducted at 16 sites in 9 countries (Bulgaria, Macedonia, Hungary, Serbia, Turkey, Czech Republic, Poland, Russia, and Ukraine).

Trial Design

Patients aged 18 or older who met criteria for narcolepsy with cataplexy based on the International Classification of Sleep Disorders–Second Edition (ICSD-2), had experienced at least 3 weekly cataplexy attacks for 1 month, and scored ≥ 12 on the Epworth Sleepiness Scale were eligible to be enrolled in the study. Female patients of child-bearing potential were required to use a medically effective method of birth control. Patients with other conditions that could account for EDS were excluded from the trial. Patients with a recent history of substance use disorders were also excluded. Additional exclusion criteria included seizure disorder, severe hepatic or renal impairment, long QTc syndrome or serious electrocardiogram abnormality,

other clinically significant physical illness, moderate or severe psychosis, bipolar disorder, severe depression (BDI ≥ 16), suicidal risk (score > 0 on BDI item G), severe anxiety, moderate or severe dementia, previous adverse reaction to central nervous system (CNS) stimulants, known hypersensitivity to the study medication or excipients, and inability to tolerate or metabolize lactose (because of the presence of lactose in investigational treatments). Concurrent use of hypnotics, tranquilizers, sedating antihistamines, benzodiazepines, anticonvulsants, amphetamines, methylphenidates, modafinil, other CNS stimulants, tricyclic antidepressants, or clonidine was not permitted in the study.

A centralized randomization system (IWRS) of ARONE was used in this study. The random list was generated by an independent company (b) (4)). Patients entered the randomization system as soon as they were screened and were assigned a patient number. Patients and investigators were blinded to the treatment assignment. Pitolisant and placebo were provided as capsules that were identical in appearance and taste and were packaged in identical blister packs. Compliance with treatment was evaluated at each visit by counting the number of capsules remaining in the blister pack and asking patients whether they had taken the investigational treatment as prescribed.

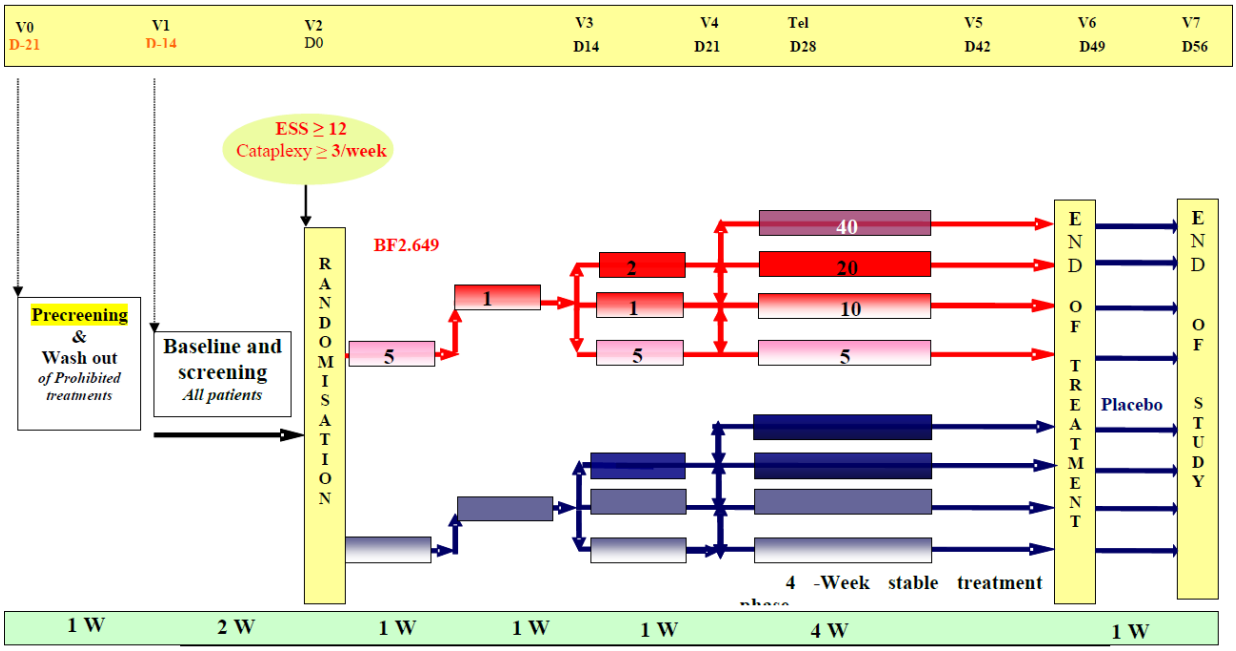
Criteria for withdrawal from the study included voluntary withdrawal of informed consent, loss to follow-up, use of unauthorized treatments, non-compliance or major protocol deviation, serious adverse event that rendered continued participation unsafe. Withdrawn patients were not replaced in the study.

Pitolisant doses ranged from 10 mg to 40 mg in the study. The Applicant's analysis of phase 2 study data indicated that repeated doses of 20 mg and 40 mg were well tolerated after a titration period and that the minimum effective dose in patients with narcolepsy is 20 mg. Furthermore, the Applicant's analysis of data from studies HARMONY I (P07-03) and HARMONY III (P09-10) indicated that the 40 mg dose would be effective for treatment of excessive daytime sleepiness and for cataplexy.

HARMONY CTP included a 1-week washout period during which patients discontinued stimulants, modafinil, or other treatments for excessive daytime sleepiness. If patients had been taking stable doses of purportedly anti-cataplectic medications (including sodium oxybate, selective serotonin reuptake inhibitors, norepinephrine reuptake inhibitors, and serotonin and norepinephrine reuptake inhibitors) for at least 1 month prior to the trial, they could continue taking their current dose during the trial. After the 2-week screening period, eligible patients were randomized 1:1 to receive either pitolisant (starting dose of 5 mg) or placebo for 1 week. The following week, patients were titrated to 10 mg of pitolisant or placebo. The following week (Day 14), doses could be adjusted by the investigators to improve efficacy and tolerability. Patients could receive 5 mg, 10 mg, or 20 mg of pitolisant or placebo; no other specific recommendations regarding dose adjustments were given to the investigators. On Day 21, doses could be adjusted again at the discretion of the investigator to the perceived optimal dose; patients could receive 5 mg, 10 mg, 20 mg, or 40 mg. Patients remained on this final dose for the duration of the 4-week stable dose phase. During a 1-week withdrawal phase, patients

in all groups received placebo. The schematic (provided by the Sponsor) in the following table summarizes the study design (Figure 6).

Figure 6: Study Design - HARMONY CTP (P11-05)



Study Endpoints

The primary endpoint in HARMONY CTP was the change in the average number of cataplexy attacks per week between the 2 weeks of baseline and the 4 weeks of the stable dose phase. Patients kept daily records of cataplexy outcomes in their cataplexy and sleep diaries.

No additional primary or key secondary endpoints were pre-specified in the study protocol. Secondary endpoints included weekly rate of cataplexy during the last 2 weeks of treatment, proportion of patients with a high cataplexy frequency (> 15 events/week), ESS, proportion of ESS responders, MWT, number of days with hallucinations, CGI-C, EQ-5D, and patients' global opinions on the effect of the drug. Evaluation of safety included adverse event recordings, vital signs, physical examinations, laboratory evaluations, monitoring of sleep quality through sleep diaries, electrocardiograms, BDI-SF, assessment of withdrawal symptoms, and patients' global opinions on the safety of the drug.

Physical examination and laboratory assessments were conducted at baseline and at the end of the treatment. Patients underwent electrocardiograms during each in-person study visit. The MWT was conducted at the start and end of treatment. The ESS was administered at each in-person study visit. Patients' sleep diaries, adverse event recordings, and BDI-SF scores were reviewed throughout the study.

Table 15 (provided by the Sponsor) summarizes the schedule of assessment activities in the study.

Table 15: Schedule of Assessments - HARMONY CTP (P11-05)

Visit	V0 Prescreening & wash out period *(Treated patients)*	V1 Screening & Baseline visit	V2[5] Treatment Start	V3	V4	Phone contact	V5	V6[5] End of treatment [(1)]	V7 End of study
Study day	D-21	D-14	D0	D14 ± 2 days	D21 ± 2 days	D28	D42 ± 2 days	D49 ± 2 days	D56 ± 2 days
Informed consent	X								
Medical interview	X	X	X	X	X	X	X	X	X
Vital signs [(2)]		X	X	X	X		X	X	X
ECG		X	X	X	X		X	X	X
Physical examination		X						X	
Lab tests [(3)]		X						X	X
Selection criteria		X	X						
ESS		X	X	X	X		X	X	X
MWT 40 mn (4 sessions)			X					X	
CGI-Severity on EDS and Cataplexy		X	X						
CGI-Change on EDS and Cataplexy				X	X		X	X	X
BDI		X	X		X			X	X
EQ-5D			X		X			X	
Patient's global opinion					X		X	X	X
Delivery of sleep diary		X	X	X	X		X	X	
Review of sleep diary			X	X	X		X	X	X
Adverse events			X	X	X	X	X	X	X
Dispensation of study drugs			X	X	X		X	X	
Drug accountability [(4)]				X	X		X	X	X
Withdrawal symptoms questionnaire									X

(1) The premature withdrawal of study visit should be conducted within a maximum of 3 days after the last dose of study drug, if possible.

(2) Vital signs include blood pressure, heart rate and body weight.

(3) Laboratory parameters including: blood cell count, platelets, urea, prothrombin ratio (PR) or factor V, creatinine, AST, ALT, GGT, alkaline phosphatases, total bilirubin, glucose, cholesterol, triglycerides, Na, K, Cl, Ca and serum pregnancy test for woman of childbearing potential.

(4) At each visit, the patient shall bring back his treatment and sleep diary.
Source – Protocol, HARMONY CTP (P11-05), Study Flow Chart, page 16

Statistical Analysis Plan

Clinical trials for this NDA were conducted entirely in Europe without prior guidance from the FDA. Therefore, the Applicant and the FDA had not reached agreement on the statistical plan before it was finalized. Semhar Ogbagaber, Ph.D. conducted the statistical review of the NDA application. For a detailed evaluation of the SAP, please refer to Dr. Ogbagaber's review.

Study populations: The Applicant included all randomized patients who received at least one dose of the drug in their modified intention to treat population. All randomized patients, regardless of whether they received treatment, were included in the extended Intent-to-Treat population. Patients who remained in the study until at least V6 without major protocol violations were included in the Per-protocol population.

Missing data: Estimation for missing values were made by carrying the arithmetic mean of the last two values forward. For patients who did not have any post-baseline values, the final value was assimilated with baseline.

Statistical Methodology for the Primary Efficacy Analysis: In the primary efficacy analysis, the Applicant conducted an analysis of covariance with a non-linear mixed effect model to compare the differences in the change in the weekly rate of cataplexy episodes between pitolisant and placebo. Statistical significance was defined as $p < 0.05$.

Statistical Methodology for Secondary Analyses: The statistical analysis plan did not include a plan to prospectively assess secondary endpoints with control of the Type-I error rate. The Applicant conducted an analysis of covariance to test the treatment effect on the ESS score. MWT results were analyzed using a Student t-test. At the request of the biometrics reviewer, MWT results were also analyzed using a Mann-Whitney non-parametric test. Aggregate scores of secondary endpoints (z-scores) were analyzed with an analysis of covariance model.

Protocol Amendments

In addition to correction of typographical errors and other minor edits and clarifications, substantive amendments to the study protocol included the addition of the option to increase pitolisant dose to 40 mg at Visit 4 in the case of inadequate improvement and updates to the statistical analysis plan, including:

- Addition of a composite score (z-score) to assess overall efficacy on cataplexy and EDS
- Addition of a supplementary dose analysis of the effect of the 20 mg or 40 mg as compared to placebo

- Addition of an analysis of interactions with concomitant anti-cataplectic treatments
- Specification that a futility analysis would be conducted when at least 40 patients were available (instead of 15 and 30 patients).

6.2.2 Study Results

Compliance with Good Clinical Practices

The Applicant has provided attestation that HARMONY CTP was conducted in accordance with Good Clinical Practice (GCP).

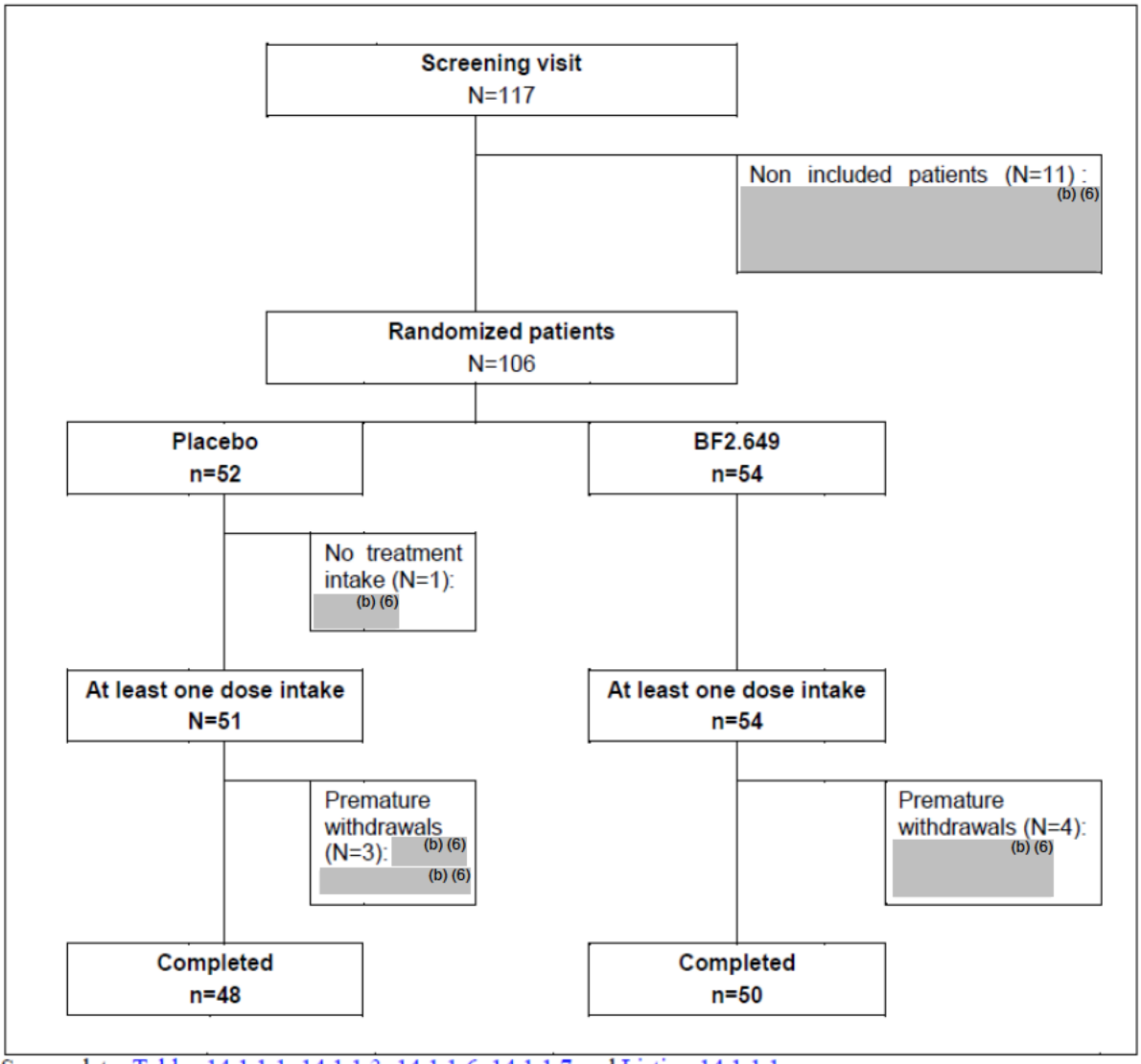
Financial Disclosure

The Applicant has adequately disclosed financial interests and arrangement with clinical investigators. The Applicant did not disclose any interests or arrangements that raised questions about the integrity of the study data.

Patient Disposition

54 patients were randomized to receive pitolisant and 52 patients were randomized to receive placebo. One patient in the placebo group decided to withdraw from the study prior to receiving any treatment. Of the remaining 51 patients in the placebo group, one patient withdrew prematurely because of a protocol deviation (did not arrive for a scheduled study visit), one patient withdrew because of lack of efficacy and patient request, and one patient withdrew because of patient request alone. Of the 54 patients in the pitolisant group, one patient withdrew because of lack of efficacy, adverse event, and patient request, one patient withdrew because of lack of efficacy and patient request, and two patients withdrew because of patient request alone. A total of 98 participants (48 in the placebo group and 50 in the pitolisant group) completed the study (Figure 7).

Figure 7: Disposition of Patients - HARMONY CTP (P11-05)



Source data: Tables 14.1.1.1; 14.1.1.3; 14.1.1.6; 14.1.1.7 and Listing 14.1.1.1

Protocol Violations/Deviations

The Applicant reported protocol deviations in seven patients who had less than 80% compliance with treatment during visit intervals. One patient in the pitolisant group reported > 120% adherence to treatment. One patient in the pitolisant group did not have a serum pregnancy test at screening; this patient was using a barrier contraceptive method and had negative serum pregnancy tests at V6 and V7. Minor protocol deviations related to the time window between visits occurred in half of patients in both the placebo and pitolisant groups.

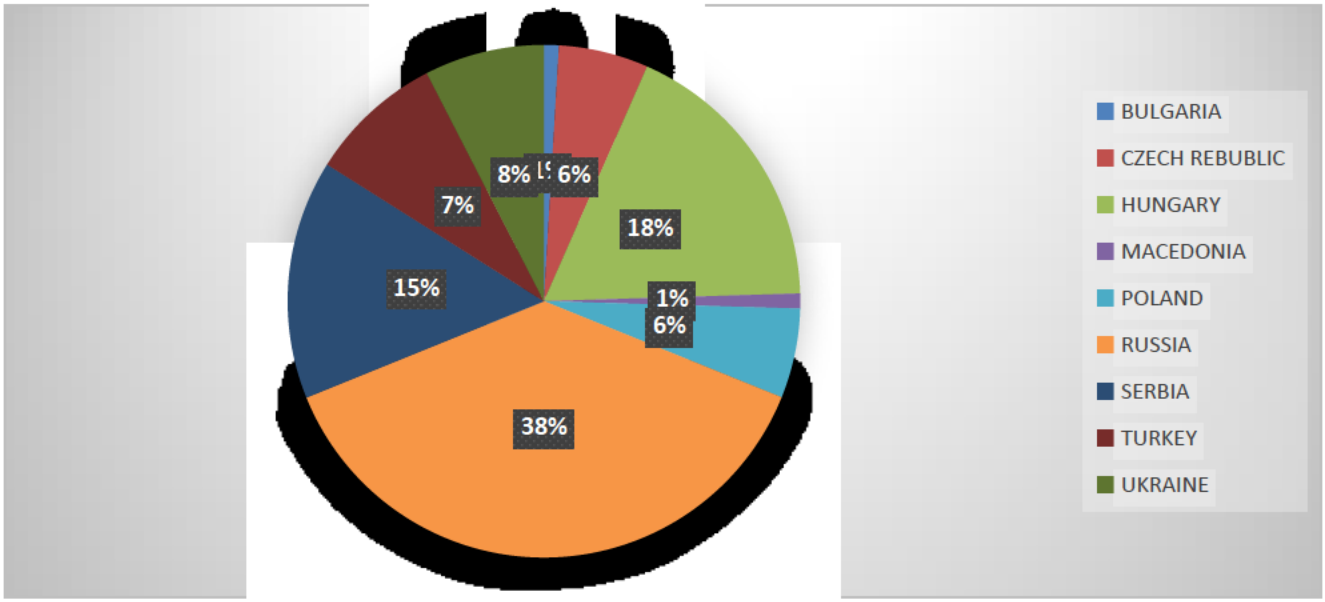
Table of Demographic Characteristics

The pitolisant and placebo groups had comparable demographic characteristics (**Table 16**). Race and ethnicity were not recorded in this trial. Most study participants were located in Russia, Hungary, and Serbia (**Figure 8**).

Table 16: Demographic Characteristics of Study HARMONY CTP (P11-05)

Demographic Parameters	Pitolisant (N= 54)	Placebo (N = 51)
Sex		
Male (%)	26 (48.1)	27 (52.9)
Female (%)	28 (51.9)	24 (47.1)
Age		
Mean years (SD)	35.8 (12.1)	38.5 (12.9)
Median (years)	34	39
Min, max (years)	18, 64	18, 66
Race	Not reported	Not reported

Figure 8: Study Participants by Country - HARMONY CTP (P11-05)



Other Baseline Characteristics

The mean baseline ESS score was 17.4 in the pitolisant group and 17.3 in the placebo group. The mean baseline number of cataplexy episodes per week was 11 in the pitolisant group and 9 in the placebo group (Table 17). A similar proportion of patients in each group were prescribed concomitant medications (Table 18 and Table 19). Five patients in the pitolisant group reported a prior medical history of depression or anxiety; no patients in the placebo group reported a history of psychiatric illness. However, one patient in the placebo group was prescribed escitalopram, reportedly for depression. One patient in the pitolisant group was prescribed fluoxetine for depression and One patient in the pitolisant group was prescribed citalopram for anxiety. The groups were otherwise similar in terms of reported past medical history.

Table 17: Baseline Disease Characteristics - Harmony CTP (P11-05)

	PLACEBO (N=51)		BF2.649 (N=54)		
Parameter	n	MN ± SD % (n/N)	n	MN ± SD % (n/N)	P-value
Number of cataplexy episodes at V0	51	9.2 ± 8.8	54	11.0 ± 8.9	0.314
History of Associated Symptoms					
Hallucinations	.	62.7 (32/51)	.	66.7 (36/54)	0.674
Ongoing Hallucinations	.	52.9 (27/51)	.	59.3 (32/54)	0.514
Automatic Behavior	.	27.5 (14/51)	.	29.6 (16/54)	0.805
Ongoing Automatic Behavior	.	25.5 (13/51)	.	24.1 (13/54)	0.867
Dyssomnia	.	62.7 (32/51)	.	68.5 (37/54)	0.533
Ongoing Dyssomnia	.	60.8 (31/51)	.	61.1 (33/54)	0.973
Sleep Paralysis	.	62.7 (32/51)	.	59.3 (32/54)	0.714
Ongoing Paralysis	.	58.8 (30/51)	.	44.4 (24/54)	0.141
Mean Sleep Latency Time at V0	51	7.8 ± 7.8	54	6.9 ± 7.7	0.549
ESS at V1	51	17.1 ± 3.4	54	17.3 ± 3.3	0.716
CGI – EDS at V1					
Mildly ill	.	2.0 (1/51)	.	1.9 (1/54)	0.885
Moderately ill	.	25.5 (13/51)	.	29.6 (16/54)	
Markedly ill	.	47.1 (24/51)	.	37.0 (20/54)	
Severely ill	.	23.5 (12/51)	.	29.6 (16/54)	
Among the most extremely ill patients	.	2.0 (1/51)	.	1.9 (1/54)	
CGI – Cataplexy atV1					
Mildly ill	.	7.8 (4/51)	.	11.1 (6/54)	0.663
Moderately ill	.	29.4 (15/51)	.	37.0 (20/54)	
Markedly ill	.	39.2 (20/51)	.	38.9 (21/54)	
Severely ill	.	17.6 (9/51)	.	9.3 (5/54)	
Among the most extremely ill patients	.	5.9 (3/51)	.	3.7 (2/54)	
BDI – 13 Item Score at V1	51	5.3 ± 4.3	54	5.3 ± 4.1	0.946
BDI – Item G at V1	51	0 ± 0	54	0 ± 0	.

Source – HARMONY CTP Clinical Study Report, Table 11.2-2, Summary of Baseline Narcolepsy and Cataplexy Characteristics, page 80

Table 18: Patients Receiving Concomitant Medications - HARMONY CTP (P11-05)

Number of Patients Receiving Concomitant Medications	N	%
Pitolisant	22	40.7%
Placebo	23	45.1%

Except for the cases noted above, antidepressants were prescribed for their purported anti-cataplectic activity. Two patients in the pitolisant group and five patients in the placebo group

received concomitant antidepressants. One patient in each group was concomitantly prescribed sodium oxybate for cataplexy.

Table 19: Concomitant Medications - HARMONY CTP (P11-05)

Concomitant Medication (Class)	Pitolisant	Placebo
INTRAUTERINE CONTRACEPTIVES	9.3%	3.9%
NATURAL AND SEMISYNTHETIC ESTROGENS, PLAIN	9.3%	5.9%
PROGESTOGENS AND ESTROGENS, FIXED COMBINATIONS	7.4%	7.8%
BETA BLOCKING AGENTS, SELECTIVE	5.5%	2%
ANILIDES[1]	3.7%	2%
BETA BLOCKING AGENTS, SELECTIVE, AND OTHER DIURETICS	3.7%	0
HMG COA REDUCTASE INHIBITORS	3.7%	3.9%
SELECTIVE SEROTONIN REUPTAKE INHIBITORS (SSRIs)[2]	3.7%	0
SYMPATHOMIMETICS, PLAIN[3]	3.7%	0
ADRENERGICS IN COMBINATION WITH CORTICOSTEROIDS OR[4]	1.9%	3.9%
PLATELET AGGREGATION INHIBITORS EXCL. HEPARIN	1.9%	3.9%
PREGNADIEN DERIVATIVES	1.9%	2%
PROTON PUMP INHIBITORS	1.9%	3.9%
SELECTIVE BETA-2-ADRENORECEPTOR AGONISTS	1.9%	3.9%
ANGIOTENSIN II ANTAGONISTS, PLAIN	0	3.9%
OTHER ANTIDEPRESSANTS[5]	0	9.8%

1. Anilides - paracetamol, paracetamol/phenylephrine
2. SSRIs - citalopram, fluoxetine
3. Sympathomimetics – tetrahydrozoline, xylomethazolin (decongestants)
4. Adrenergics in combination with corticosteroids – budesonide-formoterol, fluticasone-salmeterol
5. Other antidepressants - venlafaxine, reboxetine

*1 patient in the placebo group received sodium oxybate

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

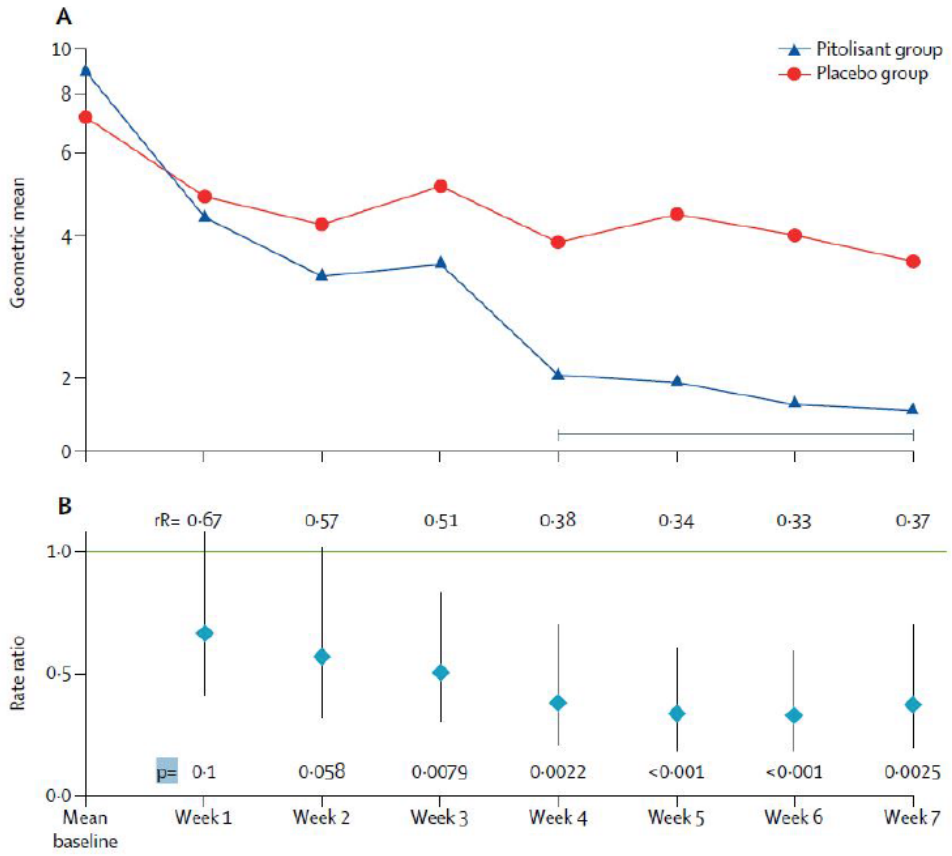
The proportion of patients who met the Applicant's definition of treatment compliance (intake of 80% to 120% of prescribed treatment) did not differ between the treatment groups and ranged from 88% to 98% at each visit.

Efficacy Results – Primary Endpoint

The Applicant's analysis of the primary efficacy endpoint, the change in the average number of cataplectic events per week (WRC) from baseline to the end of the stable dose period, demonstrated that pitolisant had a statistically significant effect ($p < 0.0001$) (Figure 9). At baseline, mean WRC was 9.2 in the pitolisant group and 7.3 in the placebo group. During the stable dose period, mean WRC was 2.3 in the pitolisant group and 4.4 in the placebo group. FDA analysis was generally concordant with the Applicant's findings. Please see biometrics review for full details of the FDA analysis.

Reviewer comment: Weekly rates of cataplexy decreased by 38% in the placebo group for reasons that are unclear. Cataplexy can be triggered by stress, and it is possible that the structure and support provided by clinical trial participation, in addition to the prospect of receiving a new treatment, reduced stress levels in some participants. Patients in the pitolisant group did however achieve a markedly greater reduction in cataplexy rates as compared with placebo.

Figure 9: Changes in Weekly Rate of Cataplexy - HARMONY CTP (P11-05)



ITT = Intent-to-treat
(A) Geometric mean of weekly cataplexy rates. (B) Rate ratio of pitolisant compared to placebo adjusted for baseline differences (mean of Weeks 1 and 2) with 95% CI and p values for each week. These data were calculated without missing values imputation.
Source: Szakacs et al. 2017 and HARMONY CTP CSR Figure 11.4:1.

Source – Clinical Study Report, HARMONY CTP (P11-05), Figure 11.4, page 87

Data Quality and Integrity

The Monitors of [redacted] (b) (4) conducted visits to each study site before patient enrollment and periodically throughout the study. Source documents were reviewed for alignment with case report forms (CRFs).

Efficacy Results – Secondary and other relevant endpoints

WRC in last 2 week and WRC > 15: The Applicant analyzed the WRC in the last 2 weeks in the pitolisant and placebo groups. Pitolisant-treated patients had a WRC in the last 2 weeks that was half that of the placebo group (95% CI [0.43, 0.63]; p < 0.0001). The Applicant also assessed the proportion of patients with WRCs > 15 at the end of treatment. While approximately 18% of patients in the placebo group and 28% in the pitolisant group had WRCs > 15 at baseline, at stable dose 24% of patients in the placebo group and 6% of patients in the pitolisant group had WRCs > 15 (p = 0.0044).

ESS and ESS Responders: Mean baseline ESS scores were similar in the pitolisant and placebo groups (17.4 and 17.3, respectively). After treatment, the Applicant found that the mean ESS score was significantly lower in the pitolisant group (12 ± 5.4) than in the placebo group (15.4 ± 5). The placebo-subtracted difference in ESS scores was -3.42 (95% CI [-5.03, -1.92]; p< 0.0001). The Applicant also found a greater proportion of responders (ESS < 10) among pitolisant-treated patients (39.2%) as compared to placebo-treated patients (18%) with a calculated odds ratio (OR) of 3.28 (95%CI [1.08, 9.92]; p = 0.035). The results of this analysis were not significant in the per-protocol population.

MWT: Sleep latency as measured by the MWT increased significantly in the pitolisant group. The Applicant calculated a mean ratio of MWT scores (pitolisant:placebo) of 1.78 (95% CI [1.22, 2.60]; p = 0.003).

Number of days with hallucinations: The Applicant calculated a ratio of the mean number of hallucinations per day at end of treatment to mean number at baseline for the entire intention to treat population and for patients for whom number of days with hallucinations (NHL) was > 0 at baseline. In patients with NHL > 0, end of treatment:baseline ratios were 0.39 in the pitolisant group and 0.57 in the placebo group. The adjusted risk ratio was 0.46 (95% CI [0.27, 0.79], p = 0.005).

CGI-C: The Applicant found that the mean change in CGI-C for cataplexy scores in pitolisant-treated patients compared to placebo-treated patients was -0.95 (95% CI [1.36, -0.54]; p < 0.0001).

EQ-5D: The Applicant did not find a statistically significant effect on EQ-5D scores.

Patient Global Opinion on Treatment: The Applicant found that patients in the pitolisant group were more likely to report experiencing a treatment effect (54%) than patients in the placebo group (26%, p = 0.0012).

Reviewer Comment: The ESS and the MWT were not designated as a primary or key secondary endpoint. However, the positive effect on these measures in HARMONY CTP provide supportive evidence for an effect on excessive daytime sleepiness. Pitolisant-treated patients also reported improved scores on CGI-C, which provides some information about the clinical meaningfulness

of the effect, although responses to CGI-C questions may be vulnerable to recall bias.

Dose/Dose Response

The Applicant analyzed the effect of the 20 mg dose compared to placebo and the 40 mg dose compared to placebo in the stable dose period. The relative risk of cataplexy events in the 20 mg dosing group was 0.392 (95% CI [0.270, 0.571]; $p < 0.0001$) and 0.623 in the 40 mg dosing group (95% CI [0.510, 0.761]; $p < 0.0001$).

Durability of Response

This study compared WRC at baseline and at the end of treatment and did not assess the durability of response.

Persistence of Effect

This trial did not assess the persistence of effect after treatment was discontinued.

Additional Analyses Conducted on the Individual Trial

The Applicant created a composite z-score that captured the effect on EDS and cataplexy. Please refer to the statistical review for full details of the Applicant's method for calculating z-scores. The Applicant found an adjusted effect of -1.00 (95% CI [-1.37, -0.64]; $p < 0.0001$) in the pitolisant group.

No significant difference in pitolisant effect was found in analysis of patients receiving concomitant anti-cataplectic medications.

The biometrics reviewer conducted an additional analysis to stratify treatment groups by study site. The description of this analysis (excerpted from the biometrics review) is below:

"A non-parametric test called Van Elteren (extension of Wilcoxon Rank Sum test) showed a statistically significant difference between the treatment groups when stratified by site (p=0.01). The method tests treatment effect in each stratum. Below is funnel plot that could help us visualize the reduction in average # cataplexy events by study sites.

*The funnel plot in [*Figure 10*] aids in comparing and visualizing the mean scores of clinical sites aligned according to their corresponding sample sizes. Sites with smaller sample sizes are highly variable, deviate from the overall mean and fall outside of the 95% CI.*

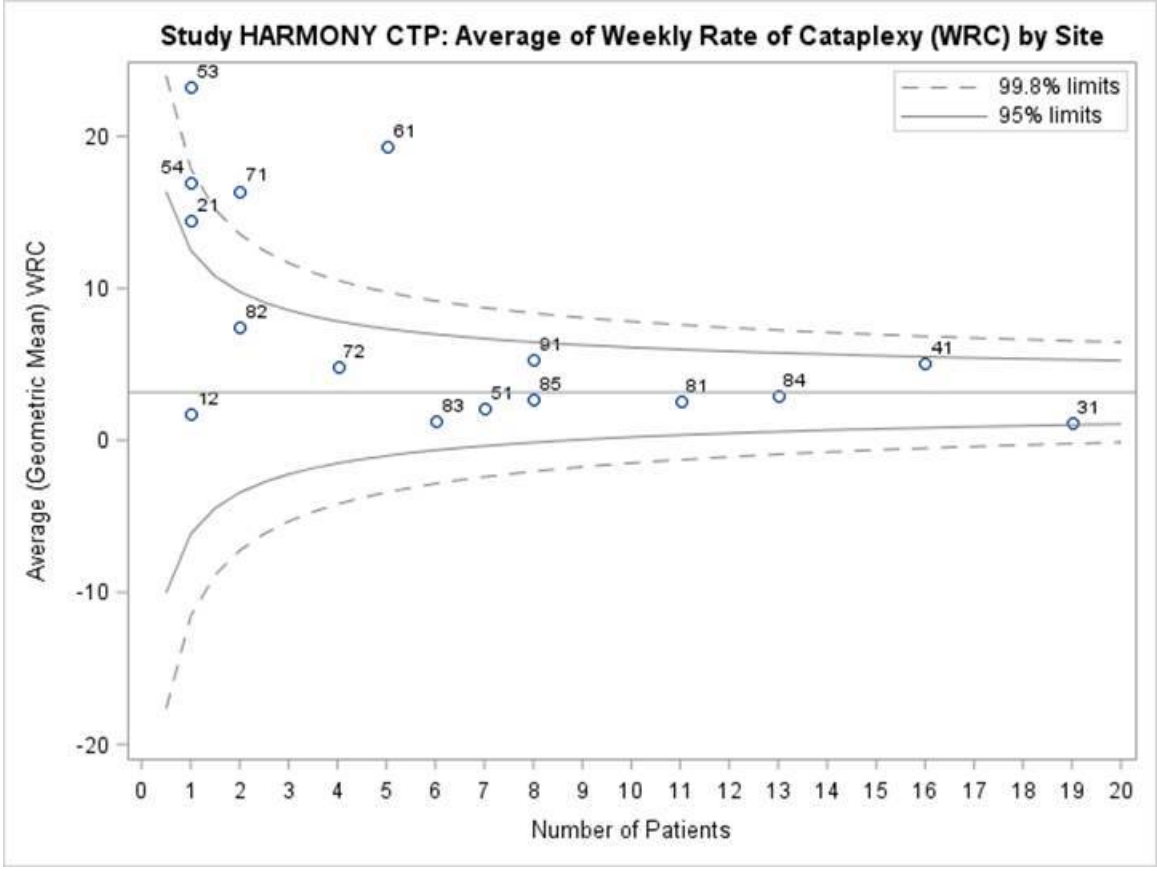
There were a number of centers with less than 5 study participants as shown in [Table 20] below."

Table 20: Sample Size by Study Site-HARMONY CTP

Study Site	N
12	1
21	1
31	19
41	16
51	7
53	1
54	1
61	6
71	2
72	4
81	11
82	2
83	6
84	13
85	8
91	8

Source: Biometrics Review, Table 27

Figure 10: Funnel Plot by Study Site for Study HARMONY CTP: Geometric Mean of the Number of Cataplexies at Every at Stable Dose [Last Four Weeks: (Wk5 + Wk6 +Wk7 + Wk8)/4]



Source: Biometrics Review, Figure 11

6.3. HARMONY I-bis (P09-15)

6.3.1. Study Design

Overview and Objective

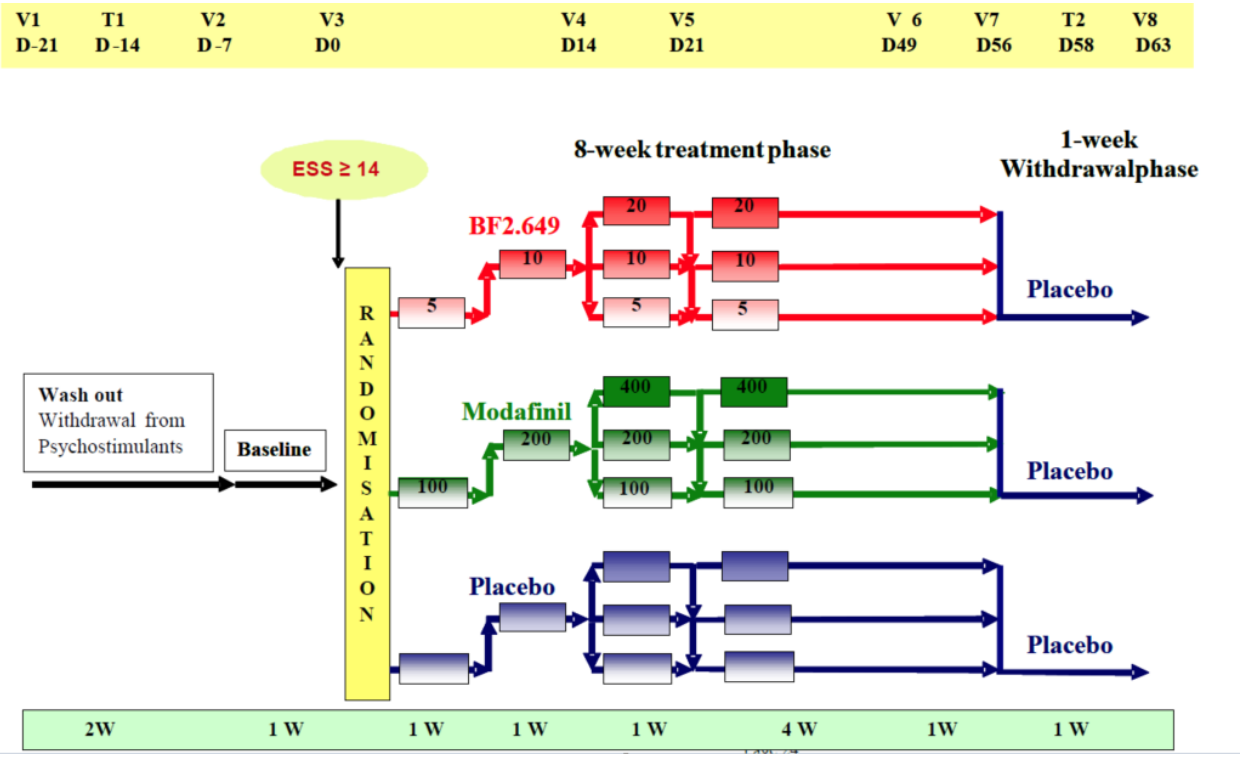
The primary objective of HARMONY I-bis (P09-15) was to determine the efficacy and safety of pitolisant administered by escalating dose (5 mg, 10 mg, or 20 mg once daily) in patients with narcolepsy and EDS as compared to placebo and modafinil.

Trial Design

HARMONY I-bis was conducted at 32 centers in Argentina (2 sites), Austria (1 site), Finland (1 site), France (8 sites), Germany (4 sites), Hungary (4 sites), Italy (6 sites), and Spain (6 sites). The design of HARMONY I-bis–including inclusion criteria and exclusion criteria, withdrawal criteria, and procedures to maintain the blind–was similar to the design of HARMONY I (described

above). HARMONY I-bis differed from HARMONY I primarily in the pitolisant dosage range (HARMONY I-bis included a pitolisant dosage range of 5 mg to 20 mg, in contrast to the 10 mg to 40 mg range in HARMONY I) and randomization ratio (patients in HARMONY I-bis were randomized to pitolisant, modafinil, or placebo in a 2:2:1 ratio, in contrast to the 1:1:1 ratio in HARMONY I). Figure 11 (provided by the Applicant) summarizes the HARMONY I-bis study design, which mirrors the HARMONY I study design.

Figure 11: Study Design - HARMONY I-bis (P09-15)



Study Endpoints

The primary endpoint in HARMONY I-bis was the ESS. No additional primary or key secondary endpoints were pre-specified in the study protocol. Secondary endpoints included the MWT, SART, ESS responder rate (final ESS score of ≤ 10 or change from baseline ≥ 3), daily cataplexy rate, CGI-C, EQ-5D, patient global opinion, and polysomnography. Safety endpoints included adverse events, BDI-SF scores, ECG, complete blood count, electrolytes, liver function tests including GGT, total bilirubin, prothrombin factor or factor V, total cholesterol, and triglycerides. Table 21 (provided by the Sponsor) describes the schedule of assessments in HARMONY I-bis.

Table 21: Schedule of Assessments - HARMONY I-bis (P09-15)

Visit	Screening (VI)	Phone Contact	Baseline (V2)	Inclusion (V3)	Titration (V4)	Titration (V5)	Control (V6)	Endpoint (V7)	Phone Contact	Withdraw (V8)	Premature dropout
Study day	D-21	D-14±1	D-7±2	D0±2	D14±2	D21±2	D49±2	D56±2	D58±1	D63±2	+3
Informed Consent	x		x (de novo)								
Narcolepsy history	x		x (de novo)								
Physical exam, ECG, lab tests	x		x (de novo)					x			x
Vital signs	x		x	x	x	x	x	x		x	x
Inclusion/non-inclusion criteria	x		x (de novo)	x							
Randomization				x							
Polysomnography				x				x			
ESS	x		x	x	x	x	x	x		x	x
CGI EDS + CGI Cataplexy			x	x	x	x	x	x		x	x
40-minute MWT				x				x			
SART				x				x			x
EQ-5D			x	x		x		x		x	x
BDI-13 items	x		x	x		x		x		x	
Adverse events					x	x	x	x	x	x	x
Delivery of sleep diary			x	x	x	x	x	x			
Review of sleep diary				x	x	x	x	x		x	x
Administration of drugs				x	x	x	x	x			
Drug accountability					x	x	x	x		x	x
Withdrawal symptoms									x	x	x
Patient's global opinion					x	x	x	x	x	x	x

1 The 3-week escalating dosage phase is followed by a 5-week stable-dose period during which dose will be 5, 10 or 20 mg/d for BF2.649; 100, 200 or 400 mg/d for Modafinil or placebo.
2 Complete biological examination including: NFS, platelets, urea, prothrombin ratio or factor V, creatinine, ALAT, ASAT, GGT, alkaline phosphatases, bilirubin, glycemia, triglycerides, total cholesterol, ionogram and serum pregnancy test for women of childbearing potential.
3 Measurement of ESS at baseline (at D-7 and at D0) and at endpoint (at D49 and at D56) will be repeated 2 times after an interval of 1 week during a visit.
4 At each visit, the patient shall bring back his treatment together with his sleep diary
5 The premature withdrawal of study visit should be conducted a maximum of 3 days after the last dose of study drug.
6 The window for V2 and V3 is + 2 days, that for V4, V5, V6, V7 and V8 is ± 2 days; that for V9 is ± 3 days
7 De novo patients could be recruited by directly entering V2. All inclusion and non-inclusion criteria should be examined during V2.
8 The item should be performed for patients without washout (period of D-21 to D-7) and without prohibited treatment within the last 15 days prior to inclusion.
9 Overnight polysomnographic recording from 10:00 p.m. until 7:00 a.m. (minimum 8 hours of recording) in the sleep laboratory the night - before V3 (at baseline) - and before V7 (at endpoint) for the first 20 patients enrolled in the first four centers.
10 The MWT will be performed again at V7, only if the MWT at V3 < 11.

Source – HARMONY I-bis Protocol, Overall Time and Events Schedule, page 24

Statistical Analysis Plan

Clinical trials for this NDA were conducted entirely in Europe without prior guidance from the FDA. Therefore, the Applicant and the FDA had not reached agreement on the statistical plan before it was finalized. Semhar Ogbagaber, Ph.D. conducted the statistical review of the NDA

application. For a detailed evaluation of the SAP, please refer to Dr. Ogbagaber's review.

Study populations: The Applicant defined the intent-to-treat (ITT population) as all randomized patients who received at least one dose of the study medication and provided at least one value after baseline. The per-protocol (PP) population consisted of patients in the IT population who remained in the study until at least Visit 6 without any major protocol deviations related to the primary endpoint.

Missing data: Estimation for missing values was made by carrying the arithmetic mean of the last two values forward. For patients who did not have any post-baseline values, the final value was assimilated with baseline.

Statistical Methodology for the Primary Efficacy Analysis: The Applicant used a linear mixed effects model to conduct the primary analysis. Statistical significance was defined as $p < 0.05$.

Statistical Methodology for Secondary Analyses: The statistical analysis plan did not include a plan to prospectively assess secondary endpoints with control of the Type-I error rate. A logistic regression model was used to analyze the ESS responder rate and a quasi-Poisson regression model was used to evaluate daily cataplexy rates. The statistical analysis plan indicated that MWT and SART results would be analyzed using a Student t-test, however in the final analysis they were analyzed using a linear fixed effect model on log (F/BL). At the request of the biometrics reviewer, the Applicant analyzed the MWT and SART results using a Mann-Whitney test.

Protocol Amendments

The study protocol was amended to increase the maximum number of participants from 125 to 185.

6.3.2. Study Results

Compliance with Good Clinical Practices

The Applicant has attested that HARMONY I-bis was conducted in accordance with Good Clinical Practice (GCP).

Financial Disclosure

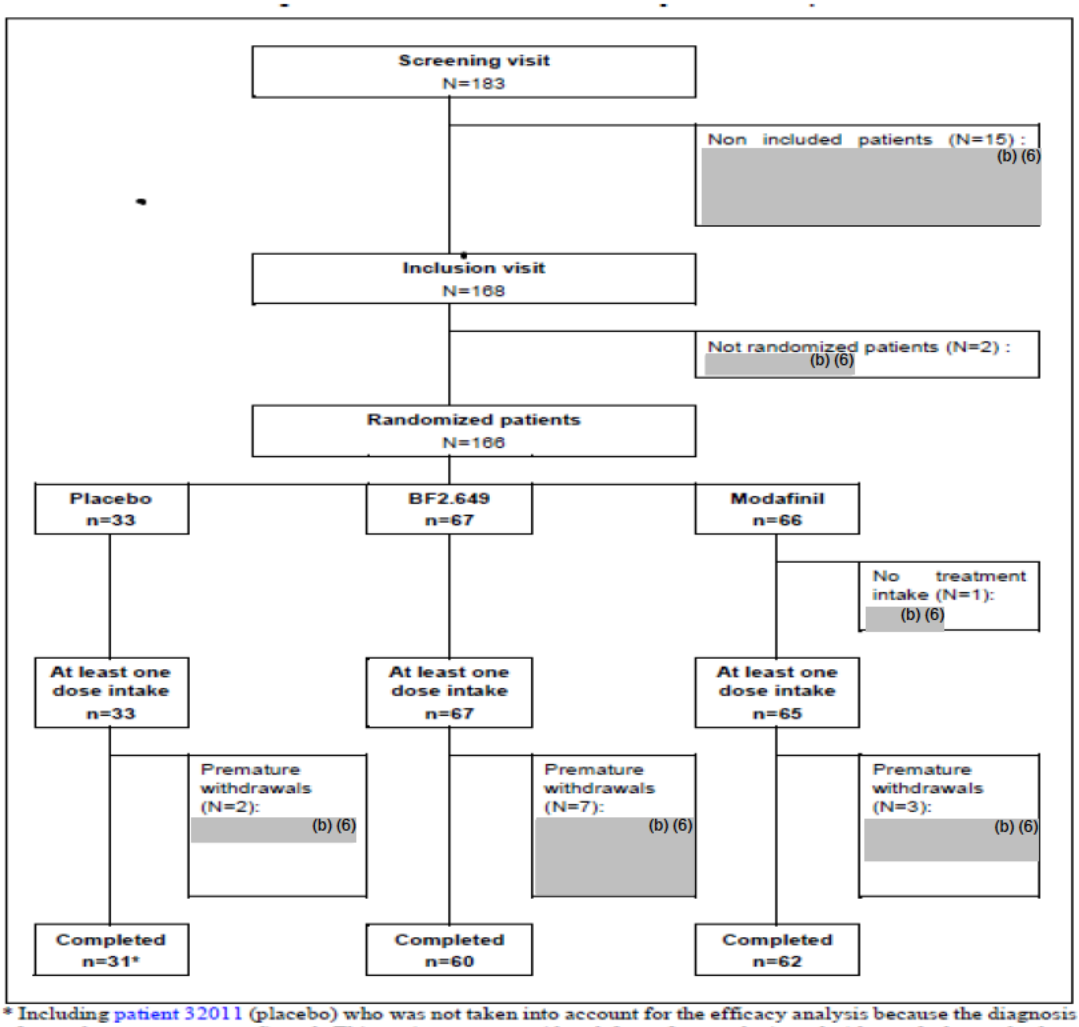
The Applicant has adequately disclosed financial interests and arrangements with clinical investigators. The Applicant did not disclose and interests or arrangements which raised questions about the integrity of the study data.

Patient Disposition

166 patients were randomized into the study: 67 in the pitolisant group, 66 in the modafinil

group, and 33 in the placebo group (**Figure 12**). One patient who was randomized into the modafinil group did not arrive for treatment intake. In the pitolisant group, five patients withdrew because of adverse events, one patient withdrew because of lack of efficacy, and one patient withdrew for personal reasons. In the placebo group, one patient was lost to follow up and one patient withdrew because of lack of efficacy. In the modafinil group, one patient withdrew because of an adverse event, one patient withdrew for personal reasons, and one patient was found to be ineligible for study participation. 90% of patients in the pitolisant group completed the trial (compared to 94% and 95% of patients in the placebo and modafinil groups, respectively).

Figure 12: Disposition of Patients - HARMONY I-bis (P09-15)



* Including patient 32011 (placebo) who was not taken into account for the efficacy analysis because the diagnosis of narcolepsy was not confirmed. This patient was considered for safety analysis as he/she took the study drug (see Section 11.1).

Protocol Violations/Deviations

The Applicant reported a single major protocol violation in HARMONY I-bis. A patient in the

modafinil group did not fulfill the inclusion criteria of ESS ≥ 14 (patient had a baseline ESS of 12). This patient was excluded from the Applicant's per protocol analysis.

Table of Demographic Characteristics

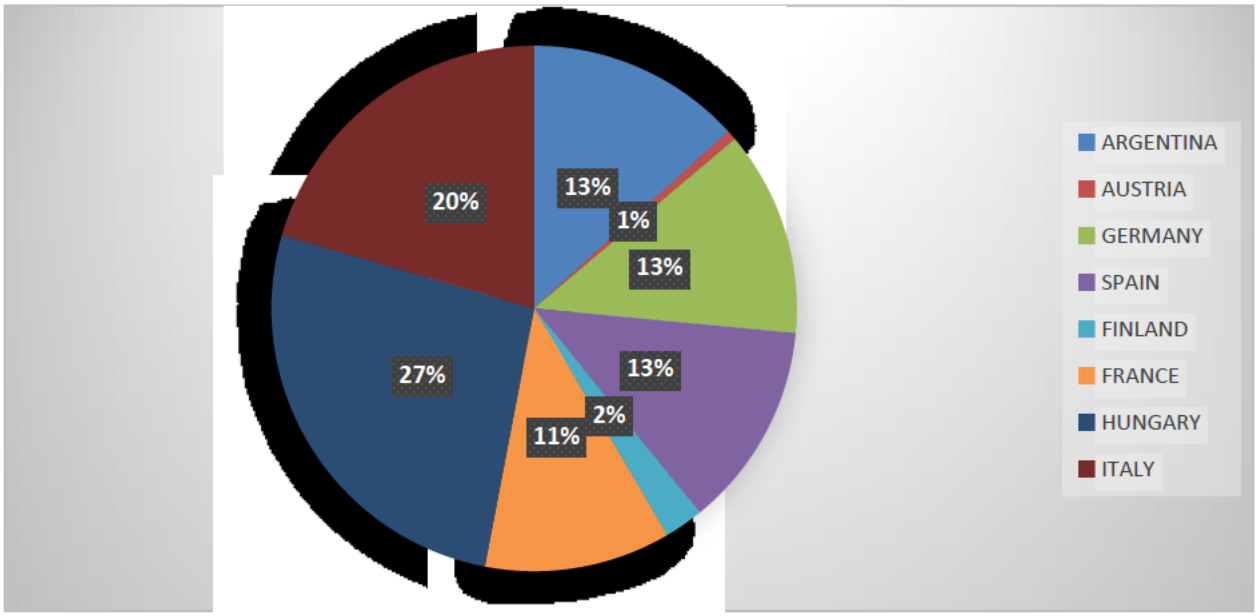
As in HARMONY 1, patients in the pitolisant group had a lower mean and median age, though the difference was not statistically significant. Demographic characteristics were otherwise comparable in the treatment groups. In all groups, greater than 80% of study participants were White.

Table 22: Demographic Characteristics of Study HARMONY I-bis (P09-15)

Demographic Parameters	Pitolisant (N= 67)	Placebo (N = 33)	Modafinil (N = 65)
Sex			
Male (%)	32 (47.8)	15 (46.9)	30 (46.2)
Female (%)	35 (52.2)	18 (53.1)	35 (53.8)
Age			
Mean years (SD)	40.7 (15.7)	43.4 (17.9)	44.1 (14.7)
Median (years)	37	42.5	43
Min, max (years)	29, 52	29, 55	32, 58
Race			
White (%)	60 (89.6)	28 (87.5)	54 (83.1)
Black or African American (%)	0 (0%)	0 (0%)	1 (1.5)
Asian (%)	0 (0%)	0 (0%)	0 (0%)
American Indian or Alaska Native (%)	1 (1.4%)	0 (0%)	0 (0%)
Native Hawaiian or Other Pacific Islander (%)	0 (0%)	0 (0%)	0 (0%)
Not Collected (%)	6 (9%)	4 (12.5%)	9 (13.9%)

Figure 13 shows the proportion of patients who participated in the study from each country. Hungary and Italy were the countries with the highest number of study participants.

Figure 13: Participants by Country - HARMONY I-bis (P09-15)



Other Baseline Characteristics (e.g., disease characteristics, important concomitant drugs)

The treatment groups were comparable in terms of baseline disease characteristics and use of concomitant medications. 75% of patients in the pitolisant group, 81% of patients in the placebo group, and 77% of patients in the placebo group had a history of cataplexy. The baseline ESS score was 18 in each treatment group. Patients in pitolisant group had a longer duration of narcolepsy (median duration of 15 years) as compared to the placebo and modafinil groups (11 and 10 years, respectively, **Table 23**). The proportion of patients receiving concomitant medications was similar in the treatment groups (**Table 24**). No patients were prescribed SSRIs or other antidepressants. One patient in each treatment group reported a prior medical history of depression. Three patients in the pitolisant group and one patient in the modafinil group reported a history of anxiety. One patient in the pitolisant group reported a history of obsessive-compulsive disorder. Two patients in in the pitolisant group and one patient in the modafinil group reported a history of obstructive sleep apnea.

Table 23: Baseline Disease Characteristics - HARMONY I-bis (09-15)

	PLACEBO (N=32)		BF2.649 (N=67)		MODAFINIL (N=65)		p-value
Parameter	**N**		**N**		**N**		
Duration of Narcolepsy [yrs], median (range)	31	11 [0; 62]	66	15 [0; 47]	63	10 [0; 59]	0.715
Multiple Sleep Latency Test (min), mean ± SD	23	5.1 ± 4	51	4.7 ± 3	55	5.3 ± 4.7	0.725
History of Cataplexy, % (n)		81.3 (26)		74.6 (50)		76.9 (50)	0.766
History of Associated Symptoms							
Sleep paralysis, % (n)		68.8 (22)		44.8 (30)		52.3 (34)	0.082
Hallucinations, % (n)		62.5 (20)		52.2 (35)		55.4 (36)	0.630
Automatic behavior, % (n)		40.6 (13)		34.3 (23)		32.3 (21)	0.718
Dyssomnia, % (n)		31.3 (10)		40.3 (27)		24.6 (16)	0.155
Baseline ESS (V2 +V3)/2, Mean ± SD	32	18.2 ± 2.3	67	18.2 ± 2.4	65	18.1 ± 2.8	0.979
Median (range)		18.5 [15; 23]		18.5 [14; 24]		17.5 [12; 24]	
Baseline MWT, gMean*	32	8.3	67	7.4	65	7.0	0.928
Median (range)		8.4 [1 ; 40]		6.5 [1 ; 40]		8.0 [0 ; 40]	
Baseline SART-NOGO, gMean*	32	7.5	67	8.2	64	8.9	0.593
Median (range)		8.4 [1; 22]		8.3 [2; 23]		10.4 [2; 22]	
Baseline SART-GO, gMean*	32	3.05	67	3.22	64	2.94	0.886
Median (range)		2.1 [1; 27.8]		2.8 [1; 38.8]		2.3 [1; 54.8]	
Baseline SART-TOTAL, gMean*	32	10.54	67	11.08	64	11.71	0.764
Median (range)		12.4 [1.3; 37.3]		10.8 [2.5; 49.5]		13 [1.8; 61]	
Baseline EQ-5D VAS, Mean ± SD	31	66.2 ± 23	67	65.1 ± 23.2	64	71.5 ± 18.3	0.208
Median (range)		74 [7.8; 100]		70 [4; 99]		75 [8; 100]	
Baseline Beck Score, Mean ± SD	32	4.5 ± 4.2	67	5 ± 4.1	65	3.5 ± 3.3	0.074
Median (range)		4 [0; 15]		4 [0; 14]		3 [0; 14]	

* gMean = geometric mean; The geometric mean was used as the data were of a log-normal distribution; which enabled avoidance of spurious influence from extreme values seen in log-normal data.
SD = standard deviation

Source – Clinical Study Report, HARMONY I-bis, Table 10, Summary of Baseline Narcolepsy Characteristics and Efficacy Variables – EIT Population, page 73

Table 24: Patients Receiving Concomitant Medications - HARMONY I-bis (P09-15)

Number of Patients Receiving Concomitant Medications	N	%
Pitolisant	22	32.8%
Modafinil	20	30.8%
Placebo	11	33.3%

No patients in the study received SSRIs or other antidepressants (Table 25). One patient in the pitolisant group developed a TEAE of anxiety, discontinued study medication, and was prescribed diazepam for anxiety. One patient in the modafinil group received an unauthorized medication, bromazepam, for blood pressure elevation. Two patients in the pitolisant group who were prescribed benzodiazepines prior to study entry discontinued these medications prior to beginning study treatment.

Table 25: Concomitant Medications - HARMONY I-bis (P09-15)

Concomitant Medication – Class	Pitolisant	Modafinil	Placebo
PROPRIONIC ACID DERIVATIVES	14.9%	9%	15.1%
ANILIDES (paracetamol)	7.5%	10.6%	3%
SALICYLIC ACID AND DERIVATIVES	7.5%	4.5%	3%
ACETIC ACID DERIVATIVES AND RELATED SUBSTANCES	4.5%	1.5%	3%
PENICILLINS WITH EXTENDED SPECTRUM	4.5%	1.5%	3%
BENZODIAZEPINE DERIVATIVES	3%	1.5%	0
HMG COA REDUCTASE INHIBITORS	3%	0	0
PSEUDOEPHEDRINE	3%	0	0
XANTHINE DERIVATIVES	3%	1.5%	0
AMIDES	1.5%	1.5%	0
PROTON PUMP INHIBITORS	1.5%	3%	6%
BIGUANIDES	0	3%	0
COMBINATIONS OF PENICILLINS, INCL. BETA-LACTAMASE INHIBITORS	0	4.5%	0
EXPECTORANTS	0	3%	3%
SODIUM OXYBATE	0	0	6%

1. Propionic acid derivatives – dexketoprofen, ibuprofen
2. Acetic acid derivatives – asceclofenac, diclofenac, (non-steroidal anti-inflammatory agents)
3. Benzodiazepine derivatives – bromazepam, diazepam
*No patients in the study received SSRIs or other antidepressants

Reviewer comment: Patients in the pitolisant group had a slightly longer duration of illness, but other baseline disease characteristics were comparable to the other groups. Pitolisant-treated patients were more likely to report a prior history of psychiatric illness, but none were prescribed antidepressant medications while enrolled in the study. A prior history of psychiatric illness could be a risk factor for developing psychiatric adverse events.

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

The proportion of patients who met the Applicant's definition of good compliance (intake of 80% to 120% of the prescribed treatment) was greater than 90% in all treatment groups.

Efficacy Results – Primary Endpoint

The mean reduction in ESS score in the pitolisant group as compared to placebo (-2.19) was statistically significant, with 95% CI of -4.17 to -0.22 and p = 0.030.

Of note, the EMA Public Assessment Report stated that clustering of small clinical study centers was not pre-planned and that results on the primary endpoint would not be significant without clustering of these centers. The Applicant clarified in a response to an information request that the clustering was in fact pre-planned. Further details, as provided in the biometrics review, are as follows:

"According to EMA Public Assessment Report analysis of the primary efficacy data by "artificially clustering" small clinical study centers, the mean ESS decrease with pitolisant showed statistically significant improvement compared to placebo (-2.19; 95% CI (-4.17, -0.22); p = 0.03). The EMA report stated pooling of centers was not pre-planned. In contrast, the SAP which was issued a month (February 13, 2013) before the database lock (March 13, 2013) included an Appendix (see Figure 14 *below) to display the random re-allocation of small centers into clusters. Analysis conducted without re-allocation of small study centers showed that pitolisant didn't demonstrate statistically significant separation from placebo (-1.94; 95% CI (-4.05, 0.07); p = 0.065). In clarifying FDA request, the applicant made clear (April 25, 2019) that the SAP for the study was amended prior to unblinding of the study."*

Figure 14: Pre-Specified Plan for Clustering of Centers - HARMONY I-BIS

APPENDIX A. CLUSTERING OF CENTERS

Source – Statistical Analysis Plan, HARMONY I-BIS, page 11

Data Quality and Integrity

Clinical trial monitoring was provided by (b) (4) for Argentinian sites and (b) (4) for the remainder of the study sites. Monitoring was performed periodically during the trial to review study enrollment and occurrence of adverse events, ensure that investigators were meeting their obligations, and to review the completeness and integrity of study records.

Efficacy Results – Secondary and other relevant endpoints

ESS responders: The Applicant defined response as a score of ≤ 10 at the end of the study or a difference between baseline and final ESS score of ≥ 3. The Applicant found that patients in the pitolisant group (65%) were more likely than patients in the placebo group (34%) to meet criteria for response (95% CI [1.35, 3.39]; p = 0.001).

Daily Cataplexy Rate: No significant difference in the daily cataplexy rate was found among patients in the three treatment groups.

MWT: The Applicant calculated a ratio of change (final:baseline) on the MWT using a linear fixed effect model and found a significant difference in the ratio of mean change between the

pitolisant group and the placebo group (1.46; 95% CI [1.06, 2.01}; p = 0.022). However, the statistical analysis plan prespecified an analysis with a Student t-test. At the request of the biometrics reviewer, the Applicant conducted an analysis with the Student t-test and a Mann-Whitney test. The results of these analyses were not statistically significant.

SART: Using a linear fixed effect model, the Applicant found that patients in the pitolisant group had lower mean SART TOTAL error (0.8) and SART NOGO error scores (0.74) compared to patients in the placebo group (1.03; p = 0.043 and 0.002, respectively). However, when analyzed using the prespecified Student t-test and a Mann-Whitney test, these results were not statistically significant.

CGI-C: CGI-C scores for EDS improved significantly more in pitolisant-treated patients than in placebo-treated patients (p < 0.001). No significant difference between the pitolisant and placebo groups on the CGI-C for cataplexy was observed.

EQ-5D and Patient Global Opinion on Treatment: No significant difference on EQ-5D scores or patient global opinion on treatment was found between the pitolisant and placebo groups.

Polysomnography: No significant differences in polysomnography parameters were observed among the treatment groups.

Reviewer comment: HARMONY I-bis provides confirmatory evidence of pitolisant's effect on EDS. This study demonstrated efficacy on the primary endpoint, the ESS. However, when results of the MWT, an objective measure of EDS, were analyzed using the statistical test that was prespecified in the analysis plan, the results were not significant. The CGI-C results suggest that pitolisant had a clinically meaningful effect on EDS, though the study did not detect a difference in quality of life scores or overall opinion on treatment in pitolisant-treated patients. No effect on daily rates of cataplexy was found in this study. The lack of effect on cataplexy events could have been related to the lower maximum dose (20 mg) as compared with the dose in HARMONY I and HARMONY CTP (40 mg).

Dose/Dose Response

The data from this single trial did not provide definitive data about dose/dose response. Please see Section 7.1.4 for full discussion of dose-response.

Durability of Response

This study compared ESS scores at baseline and at the end of treatment and did not assess the durability of response.

Persistence of Effect

This trial did not assess persistence of effect after treatment was discontinued.

Additional Analyses Conducted on the Individual Trial

Not applicable.

7. Integrated Review of Effectiveness

7.1. Assessment of Efficacy Across Trials – EDS

7.1.1. Primary Endpoints

The ESS was the primary endpoint in HARMONY I (P07-03) and HARMONY I-bis (P09-15), which were similar in study design except for the maximum allowed dose and the randomization ratio. Table 26 (adapted from a table submitted by the Applicant) summarizes the change in ESS score in the modified intent-to-treat population, which was defined as all patients who were randomized, received at least one dose of the study medication, and had at least one baseline measure. Both studies demonstrated that pitolisant had a statistically significant effect on the change in ESS score from baseline to end of treatment. The treatment duration in these studies was 8 weeks; no assessment of longer-term efficacy was conducted.

Table 26: Change in ESS Score in Narcolepsy Clinical Studies (MITT Population)

Study	**HARMONY I (P07-03)**	**HARMONY Ibis (P09-15)**	**HARMONY I (P07-03)**	**HARMONY Ibis (P09-15)**
Treatment	**Pitolisant N=31**	**Pitolisant N=66**	**Placebo N=30**	**Placebo N=32**
Max dose (mg)	40	20	-	-
Baseline ESS (mean ± SD)	17.8±2.5	18.3±2.4	18.9±2.5	18.2±2.3
End of study ESS	12.0±6.2	13.7±5.4	15.6±4.7	14.6±5.8
Treatment duration (weeks)	8	8	8	8
Changes vs. baseline[a]	-5.8±6.2	-4.6±4.6	-3.4±4.2	-3.6±5.6

ESS = Epworth Sleepiness Scale, MITT: modified Intent-to-treat; SD = standard deviation.
[a] The change in ESS from baseline to stable dosing period for a specific study arm.
Source: Applicant's Integrated Summary of Efficacy, Table 15, Changes in ESS Score in Pitolisant Studies in Narcolepsy (MITT Population), page 88

7.1.2. Secondary and Other Endpoints

Secondary endpoints in the narcolepsy clinical trials were not prespecified with a plan to control for Type-I error and were considered exploratory in this analysis. However, the results of secondary endpoint analyses did provide additional data to support the findings on the primary endpoint.

The ESS was a secondary endpoint in HARMONY CTP (P11-05), which found a statistically significant difference in the reduction in ESS scores from baseline to treatment in the pitolisant group as compared to placebo. This finding parallels the ESS results from HARMONY I and HARMONY I-bis.

HARMONY I, HARMONY CTP, and HARMONY I-bis all included the MWT as a secondary endpoint measure. HARMONY and HARMONY CTP demonstrated statistically significant improvements in sleep latency in pitolisant-treated patients as compared to placebo (Table 27). The results of the MWT in HARMONY I-bis (when analyzed using the statistical test prespecified in the analysis plan) were not statistically significant. The MWT provides additional objective data on pitolisant's effect on EDS.

Table 27: MWT Scores in HARMONY I and HARMONY CTP (MITT Population)

Visit	HARMONY I (P07-03)				HARMONY CTP (P11-05)			
	Placebo (n = 30)		Pitolisant (n = 31)		Placebo (n = 51)		Pitolisant (n = 54	
	n	GM	n	GM	n	GM	n	GM
Baseline	30	8.4	31	7.4	51	4.3	54	3.7
Final[a,]	30	7.6	31	9.7	51	4.6	54	7.1
Pitolisant vs placebo	1.47 (1.01, 2.14) p = 0.044				1.78 (1.22, 2.60) p = 0.0032			

Source: Applicant's Clinical Summary of Efficacy, Table 15, page 56

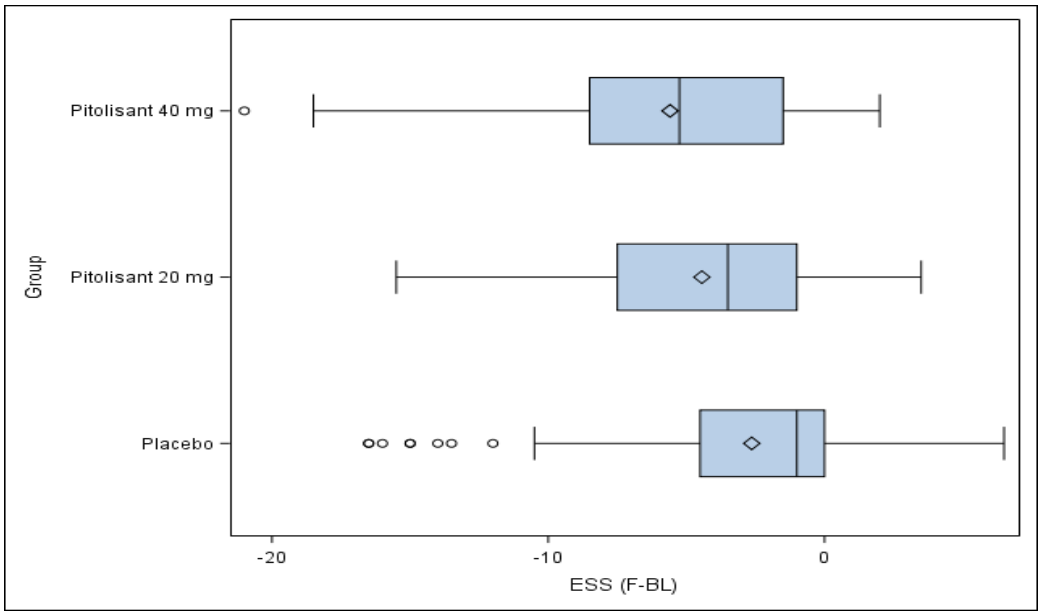
7.1.3. Subpopulations

Please see the statistical review for full details of subgroup efficacy analyses. No significant differences were observed based on age or gender for endpoints related to EDS. No subgroup analyses of racial and ethnic groups were performed given the low numbers of non-White participants in the clinical trials.

7.1.4. Dose and Dose-Response

No direct comparisons between the 20 mg and 40 mg pitolisant doses were conducted in the narcolepsy clinical trials on endpoints related to EDS. The Applicant conducted a pooled analysis of dose-response in the intent-to-treat populations (all randomized patients) in HARMONY I, HARMONY CTP, and HARMONY I-bis. Pitolisant appeared to have a linear dose-response effect (Figure 15).

Figure 15: Box Plot of Change from Baseline to Final ESS Value by Treatment Group (ITT Population)



Box = interquartile range (IQR); diamonds (◊) = mean score; vertical lines = median score; whiskers = 1.5 x IQR.
Abbreviations: BL = baseline, ESS = Epworth Sleepiness Scale, F = final, ISE = Integrated Summary of Efficacy, ITT = intent-to-treat, LOCF = last observation carried forward.
Note: LOCF method was used to handle missing data.
Source: Applicant's Integrated Summary of Efficacy, Figure 6, Box Plot of Change from Baseline to Final ESS Value by Treatment Group (ISE ITT Population), page 89

7.1.5. Onset, Duration, and Durability of Efficacy Effects

HARMONY I and HARMONY I-bis demonstrated an effect on EDS by the end of the 8-week treatment period. The long-term study (HARMONY III) submitted with this application did not include a placebo or control group and therefore could not provide conclusive data about the duration of the treatment effect.

7.2. Assessment of Efficacy Across Trials – Cataplexy

7.2.1. Primary Endpoints

HARMONY CTP demonstrated a statistically significant reduction in the weekly rate of cataplexy events (WRC) in the pitolisant group as compared to the placebo group. No other clinical trial assessed frequency of cataplexy events as a primary endpoint.

7.2.2. Secondary and Other Endpoints

HARMONY I analyzed the daily rates of cataplexy as a secondary endpoint in a subgroup of patients with a history of cataplexy and found a statistically significant effect. HARMONY I-bis failed to demonstrate an anti-cataplectic effect in a subgroup analysis of patients with cataplexy.

7.2.3. Subpopulations

No differences in efficacy based on gender or age were found for the cataplexy endpoint. The small number of non-White participants in the clinical trials precluded a subgroup analysis of racial and ethnic groups.

7.2.4. Dose and Dose-Response

No direct comparisons of the 20 mg and 40 mg were conducted in the narcolepsy clinical trials on cataplexy endpoints. Harmony I-bis, in which the maximum pitolisant dose was 20 mg (in comparison to 40 mg in HARMONY I and HARMONY CTP), failed to demonstrate an effect on cataplexy in the subgroup of patients with cataplexy who were enrolled in the trial.

7.2.5. Onset, Duration, and Durability of Efficacy Effects

HARMONY CTP examined pitolisant's effects over a 7-week treatment period. No clinical studies evaluating the durability of the effect were conducted.

7.3. Additional Efficacy Considerations

7.3.1. Considerations on Benefit in the Postmarket Setting

As noted above, the clinical trials submitted with this application did not assess long-term efficacy and do not provide information about whether the wake-promoting effect of pitolisant will diminish over time. The clinical trials also excluded patients with active physical or psychiatric illnesses and so the efficacy of pitolisant in the context of symptomatic co-morbid conditions is unknown. Patients who were pregnant were excluded from clinical trials; patients of childbearing potential were required to use contraception during the trials. However, typical onset of narcolepsy is before or during childbearing years. The clinical trials do not provide insight into whether pitolisant's efficacy at the proposed doses is impacted by pregnancy.

7.3.2. Other Relevant Benefits

Not applicable.

7.4. Integrated Assessment of Effectiveness

7.4.1. Excessive Daytime Sleepiness

The Applicant conducted two trials–HARMONY I and HARMONY I-bis–whose primary objective was to evaluate pitolisant's effect on EDS. The studies both met their primary endpoints. Secondary endpoints, including the MWT in HARMONY I, provided additional evidence in support of a meaningful clinical effect. These two trials provide adequate evidence to approve pitolisant for the treatment of EDS in narcolepsy.

7.4.2. Cataplexy

While pitolisant-treated patients in HARMONY CTP had a statistically significant reduction in WRCs compared to placebo-treated patients, no other trial assessed frequency of cataplexy episodes as a primary endpoint. Confirmatory evidence of pitolisant's effect on cataplexy should be required prior to approval. Therefore, the evidence submitted with this application is not sufficient for approval of the cataplexy indication.

8. Review of Safety

8.1. Safety Review Approach

The safety review focused primarily on three safety and efficacy studies in the narcolepsy population that compared pitolisant to placebo–HARMONY I (P07-03), HARMONY CTP (P11-05), and HARMONY I-bis (P09-15). Please refer to Section 5.1, which provides a table describing the clinical studies reviewed for this application. These studies were also used for the efficacy analysis. I examined the adverse events for each trial separately and examined pooled adverse event data after weighting the data to account for differences in the randomization ratios in the trials. I performed an analysis of the relationship of dose to incidence of adverse events. I also reviewed the pooled vital sign, laboratory, electrocardiogram, and Beck Depression Inventory databases for these studies. Based on the mechanism of action and the potential for stimulation of the adrenergic system, cardiovascular adverse events were considered adverse events of special interest. Convulsions occurred in nonclinical studies and so seizures and convulsions were also of special interest. Finally, given the psychiatric co-morbidities that often accompany narcolepsy and the product's purported downstream effects on multiple neurotransmitter systems, psychiatric adverse events were also examined closely.

I reviewed adverse events for HARMONY III (P09-10), the open-label, long-term safety study in patients with narcolepsy and for HARMONY IV (P10-01), which evaluated the safety and efficacy of pitolisant versus placebo as an add-on to sodium oxybate. In addition, I reviewed deaths and serious adverse events across the entire development program (all indications), the European Post Authorization Safety Study, the European Compassionate Use Program, and the U.S. Expanded Access Program.

European postmarketing data is publicly available in the EudraVigilance database. I reviewed the line listing of adverse events in the EudraVigilance database for years 2016 to 2019 and individual safety report forms for potentially life-threatening events, psychiatric adverse events, hepatic effects, cardiovascular events, and seizures and convulsions. In addition, the Division of Pharmacovigilance (DPV) within the Office of Surveillance and Epidemiology (OSE) assisted with a comprehensive review of the postmarketing data (see Section 8.9).
The Applicant submitted two thorough QT studies that were reviewed by the QT/IRT consultation team. In addition, FDA Controlled Substance Staff (CSS) reviewed the data for drug dependence and liability signals.

8.2. Review of the Safety Database

8.2.1. Overall Exposure

According to the ICH EI Guidance, the safety database should include at least 1500 individuals who have had exposure to the investigational product in short-term trials, 300 to 600 individuals with at least 6 months of exposure, and 100 individuals with at least 1 year of exposure. At the time of NDA submission, 1513 unique patients had been exposed to pitolisant in clinical trials. While 774 patients in clinical trials have been exposed to pitolisant for 6 months to 1 year and 334 patients in clinical trials have been exposed for ≥ 1 year, more than half of patients in the clinical development program received a dose of 20 mg once daily. Only 21% of patients in clinical trials reached 40 mg dose, which is the Applicant's recommended dose for narcolepsy (Table 28).

Table 28: Maintenance Dose Levels in Pitolisant Clinical Trials Across All Indications

Pitolisant Dose	Number of Participants
5mg	99 (6.5%)
10mg	264 (17.4%)
20mg	828 (54.7%)
30mg	1 (<1%)
40mg	315 (20.8%)
60mg	6 (<1%)
TOTAL	N=1513

*Adapted from Table 8: "Exposure to Study Medication, All Indications (ISS Safety Population)," in Applicant's Summary of Clinical Safety, page 61

The long-term safety data for the 40 mg dose is limited. In clinical trials across all indications, a total 83 patients were exposed to the 40 mg dose for 6 months to 1 year; 72 of these patients participated in narcolepsy clinical trials. A total of 62 patients in trials for all indications were exposed to the 40 mg for ≥ 1 year; 55 of these patients participated in narcolepsy clinical trials (Table 29 and Table 30).

The Applicant has estimated postmarketing patient exposure in patient-years based on sales volume of pitolisant, assuming a daily dose of 20 mg over 365 days. As reported in the Applicant's 120-day safety update, the estimated cumulative European postmarketing exposure from through February 2019 is (b) (4) patient-years.

The ongoing European post-authorization safety study (PASS, Study P15-11), which will follow patients for 5 years, has enrolled 279 patients out of a planned 300. Data collection is anticipated to be completed in 2022.

The U.S. Expanded Access Program (EAP) (HBS-101-CC-001, IND 111842) has provided pitolisant to 366 patients. Thus far, 86 patients have completed ≥ 6 months of treatment. The maximum

exposure duration in the program has been 10 months (in a single patient). 309 patients completed the titration to the 40 mg (35.6 mg) dose.

Reviewer Comment: Because of pitolisant's Orphan Drug Designation for narcolepsy, the Agency has more regulatory discretion on fulfilling ICH Exposure Guidelines.

Table 29: Duration of Exposure to Pitolisant in Narcolepsy Clinical Trials

	Number of patients exposed to pitolisant in narcolepsy clinical trials				
Dosage	< 1 month	1 to < 3 months	3 to < 6 months	6 months to < 1 year	≥ 1 year
5 mg	N= 1	N=0	N=0	N=0	N=0
10 mg	N= 22	N= 17	N=0	N=0	N=0
20 mg	N=83	N=73	N=9	N=6	N=2
30 mg	N=1	N=1	N=1	N=1	N=0
40 mg	N=196	N=179	N=89	N=72	N=55
60 mg	N=0	N=0	N=0	N=0	N=0
TOTAL	N=303	N=270	N=99	N=79	N=57

Adapted from Table 16: "Cumulative Pitolisant Exposure to Maximal Daily Dose by Duration Category – All Indications (ISS Safety Population) in the Applicant's Integrated Summary of Safety, page 57

Table 30: Duration of Exposure to Pitolisant in Trials for All Indications

	Number of patients exposed to pitolisant in all pitolisant clinical trials				
Dosage	< 1 month	1 to < 3 months	3 to < 6 months	6 months to < 1 year	≥ 1 year
5 mg	N= 47	N=0	N=0	N=0	N=0
10 mg	N= 173	N= 98	N= 66	N=51	N=18
20 mg	N=924	N=862	N=724	N=639	N=254
30 mg	N=7	N=7	N=6	N=1	N=0
40 mg	N=356	N=231	N=122	N=83	N=62
60 mg	N=6	N=0	N=0	N=0	N=0
TOTAL	N=1513	N=1198	N=918	N=774	N=334

Adapted from Table 16: "Cumulative Pitolisant Exposure to Maximal Daily Dose by Duration Category – All Indications (ISS Safety Population) in the Applicant's Integrated Summary of Safety, page 57

8.2.2. Relevant characteristics of the safety population:

The treatment groups in the safety population had similar proportions of male and female patients. Patients in the pitolisant group were younger on average than patients in the placebo and modafinil groups. Racial and ethnic background were not recorded for patients in HARMONY CTP. Patients for whom information about race and ethnicity was collected were predominantly White (Table 31). More than 70% of participants in the primary safety analysis studies came from Western European countries (Table 32).

Table 31: Demographic Characteristics of the Primary Safety Analysis Studies (HARMONY I, HARMONY CTP, HARMONY I-bis)

Demographic Parameters	Pitolisant (N= 152)	Placebo (N = 115)	Modafinil (N = 99)
Sex			
Male (%)	78 (51%)	57 (50%)	48 (48%)
Female (%)	74 (49%)	58 (50%)	52 (52%)
Age			
Mean years (SD)	38 (14.4)	40.6 (15)	42.5 (14.6)
Median (years)	35.5	40	41
Min, max (years)	18, 76	18. 79	18, 71
Age Group			
< 17 years (%)	0	0	0
≥ 17 - < 65 years (%)	144	107	93
≥ 65 - < 75 years (%)	5	5	6
≥ 75 years (%)	3	3	0
Race			
White (%)	89 (59%)	57 (49.6%)	87 (88%)
Black or African American (%)	2 (1%)	2 (1.7%)	2 (2%)
Asian (%)	0 (0%)	0 (0%)	1 (1%)
American Indian or Alaska Native (%)	1 (< 1%)	0 (0%)	0
Native Hawaiian or Other Pacific Islander (%)	0 (0%)	0 (0%)	0
Not Collected (%)	60 (39%)	56 (48.7%)	9 (9%)
Region			
Eastern Europe (%)	22 (14.5%)	19 (16.5%)	0 (0%)
Western Europe (%)	99 (65.1%)	72 (62.6%)	92 (93%)
Other (%)	31 (20.4%)	24 (20.9%)	7 (7%)
United States (%)	0 (0%)	0 (0%)	0 (0%)

Table includes patients randomized into HARMONY I, HARMONY CTP, and HARMONY I-bis
Race was not collected in HARMONY CTP (P11-05) because this information was not required for regulatory applications in the European Union. Information about race was collected in HARMONY I (P07-03) and HARMONY (P09-15).
Other regions included South America (Argentina) and Russia.

Table 32: Number of Patients Receiving Pitolisant in All Narcolepsy Clinical Trials by Country

Geographical Region n (n%)	Total Pitolisant
ECC and Assimilated	
France	128 (42.2%)
Hungary	44 (14.5%)
Germany	30 (9.9%)
Italy	22 (7.3%)
Spain	13 (4.3%)
Argentina	10 (3.3%)
Finland	8 (2.6%)
Poland	3 (1%)
Czech Republic	2 (0.7%)
Austria	1 (0.3%)
Bulgaria	1 (0.3%)
Switzerland	1 (0.3%)
Netherlands	1 (0.3%)
Other	
Russia	21 (6.9%)
Serbia	9 (3%)
Turkey	4 (1.3%)
Ukraine	4 (1.3%)
Republic of Macedonia	1 (0.3%)

Adapted from Table 24, "Baseline Characteristics – Narcolepsy Indication (ISS Safety Population), Applicant's Integrated Summary of Safety, page 76

8.2.3. Adequacy of the safety database:

The Applicant pooled data from 22 phase 2 and phase 3 studies of pitolisant in indications including narcolepsy, Parkinson's disease, Obstructive Sleep Apnea, epilepsy, schizophrenia, dementia, and ADHD into its Integrated Summary of Safety (ISS) Database. This database includes pharmacokinetic studies, phase 2 single-blind studies, phase 2 double-blind studies, phase 3 safety and efficacy studies, and open-label studies. The Applicant also created an All Narcolepsy Studies Pooling that included 8 phase 2 and phase 3 studies (P05-03, P06-06, P07-07, P09-10, P09-25, P10-01, and P11-05). Please see Appendix 13.3 for a listing and description of clinical trials.

Table 33: Grouping of Clinical Trials in Applicant's Integrated Summary of Safety Analyses

ISS Pooling	Studies
All Narcolepsy Studies	Narcolepsy: P05-03, P06-06, P07-07, P09-10, P09-15, P10-01, P11-05
All Indications	Narcolepsy: P05-03, P06-06, P07-07, P09-10, P09-15, P10-01, P11-05 Parkinson's Disease: P05-05, P07-02, P06-10, P06-11 OSA: P04-01, P05-01, P09-16, P09-08, P09-09 Epilepsy: P03-06, P04-07 Schizophrenia: P04-08 ADHD: P05-07 Dementia: P05-08

From Table 4, "Studies and Poolings, Pitolisant Integrated Summary of Safety," Applicant's Integrated Summary of Safety, page 24
ISS=Integrated Summary of Safety
OSA=Obstructive Sleep Apnea
ADHD=Attention Deficit Hyperactivity Disorder

The heterogeneity of study designs, patient populations, and indications limited the use of the Applicant's full ISS database for analysis of safety signals for the narcolepsy indication. However, the Applicant's full ISS database was reviewed for deaths and serious adverse events. This safety review focused on pooled data from HARMONY I, HARMONY CTP, and HARMONY I-bis to examine adverse events, vital signs, electrocardiograms, and Beck Depression Inventory Scores. These trials were randomized, double-blind, and placebo-controlled trials that were used for efficacy analysis for the proposed indications (b) (4). In contrast, the Applicant pooled results from HARMONY I, HARMONY CTP, HARMONY I-bis, and HARMONY IV for the Applicant's analysis of adverse events in the narcolepsy population. This safety review did examine the results from HARMONY IV; however, given that HARMONY IV evaluated the use of pitolisant as an add-on medication to sodium oxybate rather than as the primary treatment for narcolepsy, this study was not pooled with the other studies for analysis.

8.3. Adequacy of Applicant's Clinical Safety Assessments

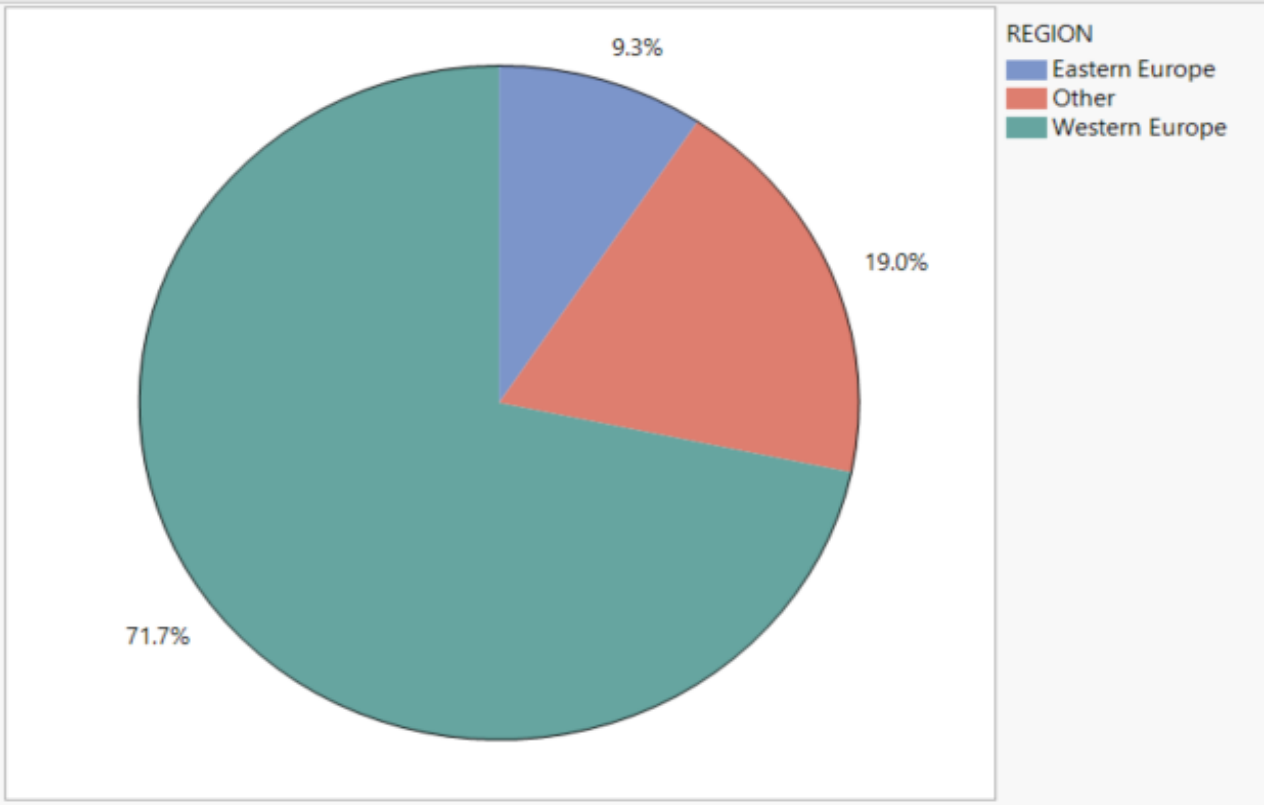
8.3.1. Issues Regarding Data Integrity and Submission Quality

The Application included Case Report Forms (CRFs) for all serious adverse events (SAEs) and adverse events leading to discontinuation in HARMONY I, HARMONY CTP, and HARMONY I-bis. No deaths occurred in the pivotal narcolepsy trials, but a CRF was submitted for a death that occurred in a long-term safety trial in patients with narcolepsy. Narratives were submitted for all deaths that occurred in the overall pitolisant clinical development program. Upon review of the adverse event databases for HARMONY I, HARMONY CTP, and HARMONY I-bis, it appears that the adverse events were coded appropriately. Data were generally presented in an organized manner that allowed for substantive review. The laboratory datasets for Studies HARMONY CTP and HARMONY I-bis (Lb.xpt, ADLB.xpt, and ADXL.xpt datasets) did not include

numerical laboratory values when originally submitted. The Applicant provided updated datasets in response to an information request.

Most adverse events in HARMONY I, HARMONY CTP, and HARMONY I-bis were reported in Western Europe, which enrolled approximately 72% of all patients in these trials. Eastern European sites enrolled 11% of patients and other regions (South America and Russia) each enrolled 17% of patients. The proportion of adverse events reported in Western Europe and Eastern Europe generally align with proportions of patients enrolled at these sites (Figure 16).

Figure 16: Adverse Events by Geographic Region in HARMONY I, HARMONY CTP, and HARMONY Ibis



Western Europe – Austria, Belgium, Czech Republic, Denmark, Finland, France, Germany, Hungary, Italy, Netherlands, Spain, Sweden, Switzerland (as defined by Applicant in ISS database)
Eastern Europe – Bulgaria, Macedonia, Poland, Serbia, Turkey, Ukraine
Other – Russia, South America

Based on a review of the adverse event database for these three studies, no systematic under-reporting of adverse events in any region or individual country was apparent.

The Applicant has also provided an analysis of adverse events in the pitolisant clinical development program (all indications) occurring in countries resembling former European Economic Community (ECC) countries versus other geographic locations. Based in part on homogeneity in narcolepsy treatment and standards of medical care, the Applicant included the

following countries in the ECC category: Argentina, Austria, Bulgaria, Czech Republic, Germany, Finland, France, Hungary, Italy, the Netherlands, Poland, Spain, and Switzerland. Countries included in the other geographic location category were Russia, Serbia, Turkey, and Ukraine. For the narcolepsy indication, no clearly significant difference in adverse event reporting between different regions was evident, although interpretation of the data is limited by the relatively small numbers of adverse events. In trials for all indications, ECC country sites were more likely than sites in other regions to report adverse events. (Table 34).

Table 34: Adverse Events by Region in Pitolisant Development Program

Patients Receiving Pitolisant in Double-Blind, Single-Blind, and Open-Label Studies		
	EEC (N=264)	Other (N=39)
	Narcolepsy Indication n (%)	
Any TEAE	150 (56.8%)	16 (41%)
Any SAE	19 (7.2 %)	0
	All Indications n (%)	
Any TEAE	841 (63.2%)	60 (32.8%)
Any SAE	86 (6.5%)	1 (0.5%)

EEC= European Economic Community
TEAE= Treatment-Emergent Adverse Event
SAE=Serious Adverse Event

8.3.2. Categorization of Adverse Events

Adverse events were coded using the Medical Dictionary for Regulatory Activities (MedDRA) version 20.0. Verbatim terms were included in the data files and translated to preferred terms that captured the full extent of the patient experience. Adverse events were categorized by PT and system organ class (SOC) in the database.

The applicant provided accurate definitions of adverse events (AEs) and serious adverse events (SAEs) in the protocol. The Applicant appropriately defined treatment emergent adverse events as events that started or worsened on or after the first dose of study medication or within 30 days following the last dose of study medication. The Applicant categorized the severity of AEs using the following scale:

- Mild – no significant interference with the subject's usual activities: acceptable, disappeared without residual effect
- Moderate – moderate interference with the subject's usual activities
- Severe – major interference with the subject's usual activities, considered as unacceptable by the physician or required specific treatment or required discontinuation from the study

Adverse events were assessed by the investigator or a member of the investigator's staff at every study visit; the last study visit occurred 1-week (± 2 days) after discontinuation of the study medication. The investigator would begin the adverse event assessment with an open-ended question such as "How are you doing (feeling)?" and would also inquire about the severity, frequency, and duration of adverse events. All adverse events were recorded on CRFs. Follow-up of the adverse event occurred until the event resolved or stabilized, even after the discontinuation of therapy. Protocols for HARMONY CTP and HARMONY I-bis indicated that period of observation for adverse events could extend to one month following the final study visit.

In HARMONY I, the investigators used the following causality assessment scale:

- Very likely – The adverse event is clearly related to the investigational drug(s). a clinical event including laboratory test abnormality, occurring in a plausible time relationship relationship to drug administration, and which cannot be explained by concurrent disease or other drugs or chemicals. The response to withdrawal of the drug (de-challenge) should be clinically plausible.

- Likely - The adverse event *is likely related* to the investigational drug(s): a clinical event, including laboratory test abnormality, with a reasonable time sequence to administration of the drug, unlikely to be attributed to concurrent disease or other drugs or chemicals. Clear-cut temporal association with improvement on cessation of study medication or reduction in dose. Reappears upon re-challenge. Follows a known pattern of response to study medication. (de-challenge)

- Possible - The adverse event *may be related* to the investigational agent(s): Follows a reasonable temporal sequence from administration: possibility that the adverse event may have been caused by the study medication but may also have been produced by the subject's clinical state or by environmental factors or other therapies administered. Information on drug withdrawal may be lacking or unclear.

- Doubtful - The adverse event *is doubtfully related* to the investigational agent(s) according to present knowledge: Does not follow a reasonable temporal sequence from administration. May have been produced by the subject's clinical state or by environmental factors or other therapies administered.

In HARMONY CTP and HARMONY I-bis, the investigators used the following causality assessment scale:

- Related / likely: Clearly related to the investigational agent / procedure, i.e. an event that follows a reasonable temporal sequence from administration of the study intervention, follows a known or expected response pattern to the suspected intervention, that is can be confirmed by improvement on stopping and reappearance

of the event after re-challenge and that could not be reasonably explained by the known characteristics of the subject's clinical state.

- Possibly related / Possible: Follows a reasonable temporal sequence from administration of the study intervention, follows a known or expected response pattern to the suspected intervention, but that could readily have been produced by a number of other factors.

- Not related / Unlikely: Clearly and incontrovertibly due only to extraneous causes and does not meet criteria listed under possible (possibly related) or likely (related).

The AE assessment strategies employed in the clinical development program were adequate and appropriate.

8.3.3. Routine Clinical Tests

In HARMONY I, laboratory assessments included complete blood count, serum sodium, potassium, chloride, GGT, ALT, AST, alkaline phosphatase, total bilirubin, prothrombin ratio or Factor V, blood urea nitrogen, creatinine, and glucose. A serum pregnancy test was performed at selection and at the end of the study for female participants. Other clinical assessments included vital signs, physical examinations, ECGs, and BDI-SF scores. Please see Table 6 for the schedule of study assessments in HARMONY I.

Clinical assessments in HARMONY CTP and HARMONY I-bis were similar to those obtained in HARMONY I but additionally included serum cholesterol and triglycerides. Please see Table 15 and Table 21 for the schedule of study assessments in HARMONY CTP and HARMONY I-bis.

Laboratory assessments were performed on-site for all studies.

The scope of clinical assessments chosen for HARMONY I, HARMONY CTP, and HARMONY I-bis were appropriate given the mechanism of action of the drug product and the known co-morbidities in the narcolepsy patient population (e.g., depression).

8.4. Safety Results

8.4.1. Deaths

The Sponsor submitted narrative summaries for all deaths that occurred in the clinical development program in the NDA and submitted an update (with one additional death) in the 120-day safety report. Nine deaths occurred in the pitolisant development program; all occurred in patients receiving pitolisant (Table 35). Of the nine deaths, six occurred in male patients. One death occurred in the open-label, long-term safety narcolepsy study (HARMONY

III, P09-10). This patient was a 73-year-old female with no co-morbid medical conditions listed who died suddenly at home. The investigator hypothesized that hot weather conditions may have contributed to her death, but no autopsy was performed to provide additional information about possible causes of death. The Sponsor reported two deaths that occurred > 30 days after study drug administration. These deaths occurred in patients with Lewy Body Dementia.

Reviewer comment: No deaths occurred in the short-term, placebo-controlled narcolepsy studies. One sudden death occurred in the open-label, long-term safety study in the narcolepsy population. The other deaths occurred in trials for Parkinson's disease, schizophrenia, and OSA. Although these patients had co-morbid health conditions that could have contributed to their risk of death, the data are insufficient to conclude whether the deaths were related to pitolisant. Most of the deaths occurred in uncontrolled, open-label extension trials that do not allow for a comparison with patients not receiving pitolisant.

Table 35: Deaths in Pitolisant Clinical Trials (All Indications)

Participant Number	Clinical Trial	Indication	Treatment	Description
(b) (6)	P09-10	Narcolepsy	pitolisant	73-year-old female with narcolepsy. Enrolled in open-label extension for 10 months when found dead at home. No autopsy performed. Investigator thought patient death could be related to hot weather conditions.
	P06-11	Parkinson's disease	pitolisant	73-year-old male with Parkinson's disease. Enrolled in open-label extension for 5 months when hospitalized for bronchopneumopathy. Died 7 days after admission.
	P06-11	Parkinson's disease	pitolisant	80-year-old male with Parkinson's disease. Enrolled in open-label extension for 9 months when hospitalized for aspiration with asphyxia. Died the day after admission.
	P09-09	OSA	pitolisant	53-year-old male with history of obstructive sleep apnea, hypertension, type II diabetes mellitus, chronic obstructive pulmonary disease, and obesity. Enrolled in open-label extension for 7 months when died at home after reporting dyspnea and abdominal discomfort. No autopsy.
	P09-09	OSA	pitolisant	58-year-old male with history of obstructive sleep apnea, hypertension, atrial fibrillation, osteoarthrosis, obesity, and metabolic syndrome. Found dead at home 2.5 months after the initiation of treatment. No autopsy was performed. Cause of death reported as acute cardiac and pulmonary insufficiency with concomitant severe OSA without continuous positive airway pressure (CPAP).
	P04-08	Schizophrenia	pitolisant	39-year-old male with history of schizophrenia, depressive episodes, prior suicide attempts. Found dead at home 2 months after randomization. Several empty boxes of medication were found.
	P15-13	OSA	pitolisant	64-year-old female with history of pneumonia, hypertension, asthma, chronic obstructive pulmonary disease, and obesity. Went into cardiac and respiratory arrest 4 days after starting pitolisant in open-label extension. No autopsy was performed. Physician diagnosis of stroke per patient's family.
	P05-08	Dementia	pitolisant	79-year-old female with Lewy Body Dementia. Completed the study and died 1 year later. Cause of death listed as disease progression.
	P05-08	Dementia	pitolisant	71-year-old male with Lewy Body Dementia, prior hospitalizations for confusional state and motor deficit, hallucinations, agitation, and aggression. Died 31 days after discontinuing pitolisant in open-label extension phase. Prior to death, had been hospitalized for pneumopathy with dysphagia. Cause of death listed as acute respiratory distress syndrome.

*Deaths occurred > 30 days after study drug administration

8.4.2. Serious Adverse Events

This section reviews in detail the Serious Adverse Events (SAEs) reported in the double-blind, placebo-controlled narcolepsy trials (HARMONY I, HARMONY CTP, HARMONY I-bis, HARMONY IV), the open-label safety extension in the narcolepsy population (HARMONY III), the U.S. Expanded Access Program (EAP), the European Post-Authorization Safety Study, and the European Compassionate Use Program (CUP). In addition, this section reviews SAEs of special interest from the full pitolisant development program.

Double-blind, Placebo-Controlled Trials: Eight SAEs occurred in HARMONY I and HARMONY I-bis; three occurred in the modafinil group, two occurred in the pitolisant group, and one occurred in the placebo group. No SAEs were reported in HARMONY CTP. No treatment-emergent SAEs were reported in HARMONY IV, which assessed the efficacy and safety of pitolisant compared to placebo as an add-on to sodium oxybate for narcolepsy.

The SAEs reported by the two patients in the pitolisant group both occurred in HARMONY I and are listed below:

- Patient (b) (6): pyelonephritis
- Patient (b) (6): hemorrhoids

HARMONY III: Seven patients reported ten SAEs in the first 12-month-period of HARMONY III, the open-label, long-term safety study. The SAEs are listed in Table 36:

Table 36: Serious Adverse Events in HARMONY III (P09-10) - Year 1

Patient Identifier	Serious Adverse Event (SAE)
(b) (6)	depression
	transient ischemic attack
	pulmonary carcinoid tumor and thoracic operation
	depression
	pregnancy and spontaneous abortion
	pregnancy and abortion
	pilonidal cyst

Patients who completed the initial 12-month-period of HARMONY III were eligible to continue treatment in a follow-up extension study. The Applicant presented data up to 5 years of treatment. The following additional SAEs occurred after the initial 12-month-period (Table 37):

Table 37: Serious Adverse Events in HARMONY III (P09-10) - Years 2 to 5

Patient Identifier	Serious Adverse Event (SAE)
(b) (6)	ovarian cyst
	gastric bypass
	trapeziectomy
	depression
	psychotic disorder, rebound psychosis, and psychiatric decompensation
	increased hepatic enzymes
	bladder operation

All Phase 3 Narcolepsy Trials: Table 38 organizes SAEs that occurred in all phase 3 narcolepsy trials (HARMONY I, HARMONY CTP, HARMONY I-bis, HARMONY IV, HARMONY III) by System Organ Class (SOC).

Table 38: Serious Adverse Events in Phase 3 Narcolepsy Clinical Trials by System Organ Class and Preferred Term

MedDRA SOC **Preferred Term**	**Double-Blind Placebo-Controlled**			**Open-Label Pitolisant (N=101) n (%)**
	Modafinil (N=98) n (%)	**Placebo (N=136) n (%)**	**Pitolisant (N=178) n (%)**	
Any SAE	3 (3)	1 (0.7)	2 (1.1)	9 (9)
Gastrointestinal disorders	**1 (1)**	**0**	**1 (0.6)**	**0**
Abdominal pain	1 (1)	0	0	0
Hemorrhoids	0	0	1 (0.6)	0
General disorders and administration site conditions	**0**	**0**	**0**	**1 (1)**
Death	0	0	0	1 (1)
Hepatobiliary disorders	**0**	**1 (0.7)**	**0**	**0**
Biliary colic	0	1 (0.7)	0	0
Infections and infestations	**0**	**0**	**1 (0.6)**	**1 (1)**
Pilonidal cyst	0	0	0	1 (1)
Pyelonephritis	0	0	1 (0.6)	0
Injury, poisoning and procedural complications	**1 (1)**	**0**	**0**	**0**
Radius fracture	1 (1)	0	0	0
Investigations	**0**	**0**	**0**	**1 (1)**

Hepatic enzyme increased	0	0	0	1 (1)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	**0**	**0**	**0**	**1 (1)**
Carcinoid tumor pulmonary	0	0	0	1 (1)
Ovarian cyst				1 (1)
Nervous system disorders	**0**	**0**	**0**	**1 (1)**
Transient Ischemic Attack	0	0	0	1 (1)
Pregnancy, puerperium and perinatal conditions	**0**	**0**	**0**	**3 (3)**
Abortion spontaneous	0	0	0	1 (0.7)
Pregnancy	0	0	0	2 (2.2)
Psychiatric disorders	**0**	**0**	**0**	**4 (4)**
Depression	0	0	0	3 (3)
Psychotic disorder	0	0	0	1(1)
Surgical and medical procedures	**0**	**0**	**0**	**3 (3)**
Bladder Operation	0	0	0	1 (1)
Gastric Bypass	0	0	0	1 (1)
Trapeziectomy	0	0	0	1 (1)

*Includes HARMONY I (P07-03), HARMONY CTP (P11-05), HARMONY I-bis (P09-15), HARMONY IV (P10-01), and HARMONY III (P09-10)

SAEs were most frequently reported in the Psychiatric disorders SOC. As noted above, four patients in the phase 3 narcolepsy clinical trials reported SAEs in the Psychiatric disorders SOC. Psychiatric disorders are adverse events of special interest for this product. I reviewed the narrative summaries of the serious psychiatric adverse events (excluding insomnia and sleep-related adverse events) that occurred in the narcolepsy clinical trials. The case narratives are summarized below:

- (b) (6) 38-year-old male with medical history of narcolepsy with cataplexy and depression. He was hospitalized for depression from (b) (6) . He was started on a different antidepressant during the hospitalization. He continued to receive pitolisant 40 mg throughout the event. He completed HARMONY III on (b) (6), voluntarily withdrawing his consent during extension period because of perceived drug ineffectiveness.

- (b) (6) 42-year-old female with medical history of narcolepsy with cataplexy, phlebitis, pulmonary embolism, idiopathic thrombocytosis, asthma, craniopharyngioma, panhypopituitarism, diabetes mellitus, depression, and right visual field deficit. She first received pitolisant in (b) (6) and was receiving a dose of 20 mg at the time of the

event. She was hospitalized from [redacted]. Pitolisant was temporarily stopped on day of admission and subsequently restarted during hospitalization at a dose of 10mg. Her antidepressant medication (venlafaxine) was increased during the hospitalization. She was reported to have recovered by [redacted] (date not specified). Her dose of pitolisant was increased to 20 mg on [redacted] She continued to receive pitolisant 20 mg once daily until [redacted].

- [redacted]: 35-year-old female with narcolepsy with automatic behavior and hallucinations, generalized anxiety, depression, binge eating, obesity, bypass surgery, hiatal hernia, gastroesophageal reflux, obstructive sleep apnea, and hypertension. She received pitolisant 40 mg once daily from [redacted] in HARMONY III. She had previously received pitolisant 40 mg once daily from [redacted] in the HARMONY I trial and had received pitolisant through a compassionate use program ([redacted]). She was hospitalized for depression from [redacted]. Her antidepressant and antianxiety medication regimens were adjusted during the hospitalization. She was hospitalized again for depression from [redacted]. Her antidepressant and antianxiety medication regimens were again adjusted. She was reported to be improving at the time of discharge. Other adverse events reported during the study included anxiety, suicidal ideation, bronchitis, influenza, and bradycardia.

- [redacted] 25-year-old male with medical history of narcolepsy with cataplexy, hallucinations, sleep paralysis, dyssomnia, psychosis [redacted] obesity with binge eating, obstructive sleep apnea, hypertension, diabetes, hypercholesterolemia, bariatric surgery. He received pitolisant in the HARMONY III open-label extension study at varying doses from [redacted] (date unspecified), from [redacted] (date unspecified), and from [redacted]. He had also previously received pitolisant 40 mg once daily from [redacted] through a compassionate use program. The patient self-discontinued haloperidol and pitolisant in [redacted] and presented with acute psychosis in [redacted]. He was hospitalized from [redacted] and was reported to have recovered. The patient had an interruption of his antipsychotic medication in [redacted] and was hospitalized in a psychiatric facility for delirium. He was reported to have partially recovered by [redacted]. Haloperidol was again discontinued, and the patient was hospitalized for psychosis from [redacted].

Seizures and convulsions are also adverse events of special interest for this application; however, none of these events were reported as serious adverse events in narcolepsy clinical trials. Because seizures and cardiovascular events are of special interest in this development program, the SAE of transient ischemic attack (reported by one patient in the HARMONY III trial) is also notable. A summary of the case narrative is below.

- [redacted]: 60-year-old female with medical history of narcolepsy, two prior transient ischemic attacks, atherosclerosis, bilateral carotid dysplasia, hypertension, hypercholesterolemia, depression, fibromuscular dysplasia, asthma, thyroid dysfunction, angioedema, cephalalgia, and first-degree atrioventricular block at screening. She experienced sudden onset of dizziness with nausea approximately one month after the first dose of pitolisant. Accompanying symptoms included erratic gate with deviation to the right side, paresthesia of the right hemi-face, malaise, and brief loss of consciousness. Findings on clinical examination included a right carotid murmur and known muscular strength weakness on the right side; clinical examination was otherwise unremarkable. She was given a diagnosis of transient ischemic attack and discharged home on the day of presentation. She was reported to be symptom-free at the time of discharge. She continued to receive pitolisant 40 mg once daily and completed the study. Other adverse events reported during the study by this patient included prolonged QTc, nonspecific polarization abnormality, pericarditis, increased serum GGT, headache, depression, bronchitis, otitis, increased weight, and cataplexy.

Reviewer comment: This patient had a prior history of TIA and significant risk factors for TIA and stroke. The TIA resolved, and the patient was able to complete the study. No clear temporal relationship between pitolisant treatment and the onset of the adverse event is evident, although a correlation between TIA and pitolisant cannot be definitively established or ruled out based on this single case.

U.S. Expanded Access Program: Five patients with narcolepsy in the U.S. Expanded Access Program (EAP) experienced SAEs. Three of the SAEs were psychiatric adverse events (Table 39).

Table 39: Serious Adverse Events in US Expanded Access Program (EAP)

Patient Identifier	Serious Adverse Event (SAE)
[redacted]	Fall, cellulitis, and blood infection
	Worsening of lymphoma
	Alcoholic relapse
	Bipolar disorder and Suicidal Ideation
	Suicide attempt

The case narratives for the psychiatric adverse events (excluding sleep-related adverse events) in the EAP are summarized below:

- Patient [redacted] – 37-year-old woman with medical history of narcolepsy without cataplexy, suicide attempts, overdose, alcohol dependence, bipolar disorder, anxiety, depression, fibromyalgia, seizure disorder, asthma, and restless legs syndrome. She was admitted to a detoxification center approximately 4 months after starting pitolisant (which had been titrated to a dose of 40 mg). Pitolisant was discontinued because of alcohol use disorder.

- Patient [redacted] – 37-year-old male with medical history of narcolepsy with cataplexy, bipolar disorder/depression, epileptic disorder, visual impairment, hearing impairment, urinary tract infections, migraine headaches, and obesity. He was started on pitolisant on [redacted] and titrated to a dose of 40 mg. On [redacted] the patient was hospitalized for depressive symptoms, racing thoughts, anxiety, and thoughts of self-harm. The patient reportedly placed a noose around his neck and expressed that he wanted to hang himself. While hospitalized, he presented with an illogical and tangential thought process. His symptoms were characterized in the case narrative as a relapse of bipolar disorder. His symptoms resolved by his discharge on [redacted], Pitolisant was stopped on [redacted] and resumed on [redacted]

- Patient [redacted] – 19-year-old male with medical history of narcolepsy, anxiety disorder, tobacco use, nonadherence with medications, depression/bipolar disorder, suicidal ideation, and prior overdose. He began taking pitolisant on [redacted] The patient took five times his usual dose of sodium oxybate on [redacted] in the context of multiple social stressors. He was intubated for several hours in the emergency room and ultimately hospitalized for psychiatric evaluation. Pitolisant was discontinued on [redacted].

European Observational Post-Authorization Safety Study: No SAEs were reported in the European Observational Post-Authorization Safety Study (PASS) at the time of NDA submission. Two patients with narcolepsy reported SAEs in PASS study after the NDA cut-off date.

- [redacted] – Insomnia
- [redacted] – sinus tachycardia, chest discomfort, troponin elevation

European Compassionate Use Program: Two SAEs of pregnancy have been reported in patients with narcolepsy who are enrolled in the European Compassionate Use Program (CUP).

Reviewer comment: Overall, the SAEs reported in the narcolepsy clinical trials did not appear to indicate an unexpected safety signal or suggest that additional monitoring of any safety signal would be required for safe use of pitolisant. No clear signal for cardiovascular events emerged from analysis of SAEs and no seizures occurred in the clinical trials. While no serious psychiatric adverse events were reported in the double-blind, placebo-controlled clinical trials, patients in the open-label, long-term safety study and in the Expanded Access Program did report serious psychiatric adverse events including depression leading to hospitalization, bipolar disorder, and a suicide attempt. The case narratives themselves are insufficient to definitively determine if pitolisant was associated with the development of psychiatric adverse events. However, in all the cases of serious psychiatric adverse events reviewed above, patients had a history of psychiatric illness preceding exposure to pitolisant and no clear temporal relationship between the introduction of pitolisant and the worsening of their symptoms was noted.

Clinical Trials for All Indications: Table 40 (provided by the Applicant) lists serious adverse events reported in clinical trials for all indications in the pitolisant development program by SOC. The most common SOCs for SAEs were: Surgical and Medical Procedures; Injury, Poisoning, and Procedural Complications; Infections and Infestations; Nervous System Disorders; and Psychiatric Disorders.

Table 40: Serious Adverse Events by System Organ Class in Pitolisant Clinical Trials (All Indications)

MedDRA SOC **Preferred Term**	**Double-Blind Placebo-Controlled**			**Single-Blind and Open-Label Pitolisant (N=1021) n (%)**	**TOTAL Pitolisant (N=1513) n (%)**
	Modafinil (N=95) n (%)	**Placebo (N=475) n (%)**	**Pitolisant (N=1043) n (%)**		
Any SAE	3 (3.2%)	15 (3.2%)	27 (2.6%)	62 (6.1%)	87 (5.8%)
Cardiac disorders	**0**	**1 (0.2%)**	**2 (0.2%)**	**3 (0.3%)**	**5 (0.3%)**
Gastrointestinal disorders	**1 (1.1%)**	**3 (0.6%)**	**5 (0.5%)**	**1 (<0.1%)**	**6 (0.4%)**
General disorders and administration site conditions	**0**	**1 (0.2%)**	**4 (0.4%)**	**2 (0.2%)**	**6 (0.4%)**
Malaise	0	0	2 (0.2%)	0	2 (0.1%)
Hepatobiliary disorders	**0**	**1 (0.2%)**	**0**	**2 (0.2%)**	**2 (0.1%)**
Infections and infestations	**0**	**0**	**2 (0.2%)**	**5 (0.5%)**	**7 (0.5%)**
Infection	0	0	1 (<0.1%)	1 (<0.1%)	2 (0.1%)
Pyelonephritis	0	0	1 (<0.1%)	1 (<0.1%)	2 (0.1%)
Injury, poisoning and procedural complications	**1 (1.1%)**	**0**	**5 (0.5%)**	**5 (0.5%)**	**10 (0.7%)**
Fall	0	0	2 (0.2%)	0	2 (0.1%)
Hip fracture	0	0	0	2 (0.2%)	2 (0.1%)
Investigations	**0**	**1 (0.2%)**	**3 (0.3%)**	**2 (0.2%)**	**5 (0.3%)**
Musculoskeletal and connective tissue disorders	**0**	**1 (0.2%)**	**2 (0.2%)**	**4 (0.4%)**	**6 (0.4%)**
Musculoskeletal pain	0	0	2 (0.2%)	1 (<0.1%)	3 (0.2%)
Neoplasms benign, malignant and unspecified (incl cysts and	**0**	**1 (0.2%)**	**0**	**6 (0.6%)**	**6 (0.4%)**
Nervous system disorders	**0**	**3 (0.6%)**	**3 (0.3%)**	**5 (0.5%)**	**8 (0.5%)**
Parkinson's disease	0	0	2 (0.2%)	1 (<0.1%)	3 (0.2%)

Pregnancy, puerperium and perinatal conditions	**0**	**0**	**0**	**3 (0.3%)**	**3 (0.2%)**
Pregnancy	0	0	0	3 (0.3%)	3 (0.2%)
Psychiatric disorders	**0**	**4 (0.8%)**	**3 (0.3%)**	**6 (0.6%)**	**9 (0.6%)**
Confusional state	0	2 (0.4%)	1 (<0.1%)	1 (<0.1%)	2 (0.1%)
Depression	0	0	0	3 (0.3%)	3 (0.2%)
Psychotic disorder	0	0	0	2 (0.2%)	2 (0.1%)
Renal and urinary disorders	**0**	**0**	**0**	**2 (0.2%)**	**2 (0.1%)**
Respiratory, thoracic and mediastinal	**0**	**1 (0.2%)**	**0**	**5 (0.5%)**	**5 (0.3%)**
Bronchopneumopathy	0	0	0	2 (0.2%)	2 (0.1%)
Surgical and medical procedures	**1 (1.1%)**	**0**	**2 (0.2%)**	**11 (1.1%)**	**13 (0.9%)**
Deep brain stimulation	0	0	0	2 (0.2%)	2 (0.1%)
Vascular disorders	**0**	**1 (0.2%)**	**0**	**2 (0.2%)**	**2 (0.1%)**
Hypertension	0	0	0	2 (0.2%)	2 (0.1%)

ISS=integrated summary of safety; MedDRA=Medical Dictionary for Regulatory Activities; SAE=serious adverse event; SOC=system organ class
SOCs and preferred terms are listed alphabetically.
Source: ISS Table 14.3.4.1

Table 41 and Table 42 list the serious adverse events of special interest in pitolisant-treated patients in studies for all indications.

Seizures and convulsions were observed in nonclinical studies; in the clinical trials, four patients enrolled in Study 04-07, which examined the safety and efficacy of pitolisant in patients with refractory partial seizures, reported TEAEs of epilepsy. One of these patients experienced a SAE of worsening epilepsy. The case narrative for this patient is summarized below.

- (b) (6): 46-year-old male with a past medical history of partial seizures with secondary generalization was started on pitolisant 20 mg and ultimately titrated up to a dose of 30 mg. The patient was hospitalized 43 days after starting pitolisant 20 mg because of an increase in the frequency of seizures. The patient recovered and continued pitolisant.

Reviewer comment: All patients who reported TEAEs of epilepsy had a pre-existing history of seizures. No signal for new-onset seizures emerged in the clinical development program.

Death secondary to cardiopulmonary failure occurred in two patients in the OSA clinical development program; another patient died suddenly but no cause of death was identified. Of

note, one patient with OSA had a SAE of prolonged QT interval. The case narrative for this patient is summarized below.

- (b) (6): 53-year-old female with OSA who received pitolisant, titrated up to a dose of 10 mg. The patient had a QTcB interval of 443 msec at the selection visit when measured manually (460 msec with automatic measurement). The patient was hospitalized after Visit 3 because of a prolonged QTcB interval, based on automatic calculation, of 468 msec. Holter monitoring for 48 consecutive hours was unremarkable. A review of ECG records from the ECG core lab revealed that the ECG reading at Visit 3 may have been secondary to an incorrect automated calculation.

Reviewer comment: Based on the clinical information presented, the reported TEAE of prolonged QT may have been spurious. No clear signal for serious dysrhythmias or QT prolongation emerged in the clinical development program. Patients in the dementia and Parkinson's disease trials reported cardiovascular adverse events including cardiac failure, myocardial infarction, hypertension, and angina. Most of these patients had underlying risk factors for cardiovascular disease and most of these events occurred in the open-label phase of the clinical trials. Therefore, whether there is a correlation between pitolisant and these other cardiovascular events is unclear.

Table 41: Serious Psychiatric and Neurologic Adverse Events of Special Interest in Pitolisant Clinical Trials (Non-Narcolepsy Indications)

Study Number	Patient Identifier	Indication	Treatment	Serious Adverse Event (SAE)
P04-07	(b) (6)	partial seizures	pitolisant	epilepsy
P05-08		dementia	pitolisant (open-label extension)	confusional state
P05-08		dementia	pitolisant (open-label extension)	transient ischemic attack
P05-08		dementia	pitolisant (open-label extension)	confusional state, aggression, hallucination, dysphagia, aspiration pneumonia, motor dysfunction
P05-08		dementia	pitolisant (open-label extension)	confusional state, hallucination, and insomnia
P06-10		Parkinson's disease	pitolisant (open-label)	psychotic disorder
P06-10		Parkinson's disease	pitolisant	confusional state and renal failure
P07-02		Parkinson's disease	pitolisant	anxiety
P07-02		Parkinson's disease	placebo	suicide attempt

Table 42: Serious Cardiovascular Adverse Events in Pitolisant Clinical Trials (Non-Narcolepsy Indications)

Study Number	Patient Identifier	Indication	Treatment	Serious Adverse Event (SAE)
P06-10	(b) (6)	Parkinson's disease	pitolisant (open-label extension)	hypertension
P06-10		Parkinson's disease	pitolisant (open-label)	acute cardiac failure and Parkinson's disease
P06-10		Parkinson's disease	pitolisant	cardiac pacemaker insertion
P06-10		Parkinson's disease	pitolisant	cardiac failure
P06-10		Parkinson's disease	pitolisant (open-label)	angina pectoris
P06-10		Parkinson's disease	pitolisant (open-label)	myocardial infarction
P09-08		OSA	pitolisant	hypertension
P09-08		OSA	pitolisant	QT prolonged
P06-11		Parkinson's disease	placebo	chest pain
P06-11		Parkinson's disease	placebo	myocardial infarction
P06-11		Parkinson's disease	placebo	myocardial necrosis marker increased

8.4.3. Dropouts and/or Discontinuations Due to Adverse Effects

No patients in the pitolisant group in HARMONY I withdrew from the trials because adverse events; four patients in the placebo group and four patients in the modafinil group had adverse events leading to discontinuation. In HARMONY I-bis, five patients in the pitolisant group (9%) withdrew because of adverse events (**Table 43**); no patients in the placebo group and one patient in the modafinil group had adverse events leading to discontinuation. In HARMONY CTP, one patient in the pitolisant group withdrew because of an adverse event of nausea; no patients in the placebo group withdrew because of adverse events.

Table 43: Adverse Events Leading to Discontinuation in Patients Receiving Pitolisant – HARMONY I-bis (P09-15)

Patient Identifier	Treatment Group	Adverse Event Leading to Discontinuation
(b) (6)	pitolisant	anxiety and depression
	pitolisant	nervousness
	pitolisant	insomnia, hypnagogic hallucination, cataplexy, myalgia
	pitolisant	somnolence, cataplexy
	pitolisant	abdominal pain, headache
	modafinil	abdominal pain

8.4.4. Significant Adverse Events

Severe Adverse Events: One patient in the pitolisant group in HARMONY CTP (b) (6) experienced a severe adverse event of nausea. The severe adverse events occurring in HARMONY I and HARMONY I-bis are listed in the **Table 44** and

Table 45 below. Fifteen patients who received pitolisant in the three trials reported a severe adverse event compared to three patients in the placebo group.

Table 44: Severe Adverse Events in HARMONY I (P0703)

Patient Identifier	Treatment Group	Severe Adverse Event
(b) (6)	pitolisant	pyelonephritis
	pitolisant	hemorrhoids and abdominal discomfort
	pitolisant	hordeolum
	modafinil	abdominal pain
	modafinil	abnormal behavior
	modafinil	influenza
	modafinil	drug withdrawal syndrome
	modafinil	abdominal pain
	modafinil	lymphadenopathy
	modafinil	inner ear disorder
	modafinil	aortic aneurysm repair
	placebo	pregnancy
	placebo	back pain
	placebo	biliary colic

Table 45: Severe Adverse Events in HARMONY I-bis (P09-15)

Patient Identifier	Treatment Group	Severe Adverse Event
(b) (6)	pitolisant	cataplexy
	pitolisant	somnolence and cataplexy
	pitolisant	headache and abdominal pain
	pitolisant	arthralgia
	pitolisant	angina pectoris and meningitis
	pitolisant	headache
	pitolisant	cataplexy
	pitolisant	headache
	pitolisant	somnolence
	pitolisant	dyspepsia
	pitolisant	headache
	modafinil	abdominal pain
	modafinil	pain in extremity
	modafinil	pulmonary mass and somnolence
	modafinil	radius fracture
	modafinil	somnolence
	modafinil	migraine

Reviewer comment: *Patients in the pitolisant group were more likely than patients in the placebo group to report severe adverse events. However, no consistent pattern or safety signal emerged in review of the severe adverse events reported in HARMONY I, HARMONY CTP, and HARMONY I-bis. No patients in the pitolisant group reported severe psychiatric or cardiovascular adverse events.*

Adverse Events Leading to Dose Adjustment: In HARMONY I, four patients in the pitolisant group experienced adverse events that led to dose adjustment, compared to six patients in the modafinil group and seven patients in the placebo group (**Table 46**). In HARMONY CTP, six patients in the pitolisant group and two patients in the placebo group experienced adverse events leading to dose adjustment (**Table 47**). In HARMONY I-bis, ten patients in the pitolisant group, eight patients in the modafinil group, and one patient in the placebo group experienced adverse events leading to dose adjustment (Appears this way on original **Table** 48). Excluding sleep-related adverse events, eight patients in the pitolisant group in these three trials experienced psychiatric adverse events (stress, anxiety, nervousness, irritability, depression, hypnogogic hallucinations) leading to dose adjustment, compared to one patient in the placebo group. Two patients in the pitolisant group experienced cardiovascular adverse events (palpitations, hypertension, increased heart rate) leading to dose adjustment; no patients in the placebo group required dose adjustment because of cardiovascular events.

Table 46: Adverse Events Leading to Dose Adjustment - HARMONY I (P07-03)

Patient Identifier	Treatment Group	Adverse Event Leading to Dose Change	Outcome
(b) (6)	pitolisant	hemorrhoids, abdominal discomfort	drug interrupted
	pitolisant	rash	drug interrupted
	pitolisant	stress	dose reduced
	pitolisant	insomnia	dose reduced
	modafinil	abdominal pain, abnormal behavior	drug withdrawn
	modafinil	anxiety	dose reduced
	modafinil	inner ear disorder	drug withdrawn
	modafinil	aortic aneurysm repair	drug withdrawn
	modafinil	headache, chest pain	drug withdrawn
	modafinil	abdominal pain	dose reduced
	placebo	osteoarthritis, rhinitis, sinusitis	drug withdrawn
	placebo	pregnancy	drug withdrawn
	placebo	cataplexy, somnolence	dose reduced
	placebo	gastrointestinal infection	drug interrupted
	placebo	biliary colic	drug withdrawn
	placebo	renal pain, fluid retention	drug withdrawn
	placebo	visual impairment	dose reduced

Table 47: Adverse Events Leading to Dose Change - HARMONY CTP (P11-05)

Patient Identifier	Treatment Group	Adverse Event Leading to Dose Change	Outcome
(b) (6)	pitolisant	nausea	drug withdrawn
	pitolisant	palpitations, sleep disorder	dose reduced
	pitolisant	hypertension, heart rate increased, dyssomnia	dose reduced
	pitolisant	insomnia, asthenia, nausea, headache	dose reduced
	pitolisant	asthenia, anxiety	dose reduced
	pitolisant	irritability, anxiety	dose reduced
	placebo	dyssomnia, somnolence, headache	dose reduced
	placebo	somnolence, asthenia, depressed mood	dose reduced

Table 48: Adverse Events Leading to Dose Change - HARMONY I-bis (09-15)

Patient Identifier	Treatment Group	Adverse Event Leading to Dose Change	Outcome
(b) (6)	pitolisant	anxiety, depression	drug withdrawn
	pitolisant	nervousness	drug withdrawn
	pitolisant	headache	dose reduced
	pitolisant	fatigue	dose reduced
	pitolisant	anxiety	dose reduced
	pitolisant	insomnia, hypnagogic hallucination, cataplexy, myalgia,	drug withdrawn
	pitolisant	insomnia	dose reduced
	pitolisant	somnolence, cataplexy	drug withdrawn
	pitolisant	somnolence, depression, insomnia, nightmare	dose reduced
	pitolisant	abdominal pain	drug withdrawn
	modafinil	tongue movement disturbance	dose reduced
	modafinil	fatigue	dose reduced
	modafinil	increased appetite	dose reduced
	modafinil	dizziness	dose reduced
	modafinil	euphoric mood	dose reduced
	modafinil	somnolence, anxiety, nightmare	dose reduced
	modafinil	chest pain	drug withdrawn

(b) (6)	modafinil	abdominal pain	drug withdrawn
	placebo	discomfort, disorientation	drug withdrawn

Reviewer comment: *Patients in the pitolisant group were more likely than patients in the placebo group to require an adjustment or interruption in treatment during the dose-adjustment phase of the clinical trials. Patients in the pitolisant group did require dose adjustments for psychiatric and cardiovascular adverse events. Anxiety was the psychiatric adverse event most commonly associated with dose adjustment.*

8.4.5. Treatment Emergent Adverse Events and Adverse Reactions

HARMONY I (P07-03): Nervous System Disorders, Psychiatric Disorders, and Gastrointestinal Disorders were the most frequently reported SOCs for TEAEs in pitolisant-treated patients in HARMONY I (**Table 49**). The TEAEs that occurred most commonly and at a frequency greater than placebo were headache, rash, abdominal pain, and insomnia (for this analysis, insomnia and poor-quality sleep were pooled into a single adverse event category; **Table 50**).

Table 49: Treatment Emergent Adverse Events by System Organ Class - HARMONY I (P0703)

	Pitolisant (N = 31)			Placebo (N = 30)		
SOC	Events	Number of subjects	Proportion (%)	Events	Number of subjects	Proportion (%)
Cardiac disorders	2	2	6.25	0	0	0
Eye disorders	1	1	3.13	0	0	0
Gastrointestinal disorders	12	6	18.75	2	2	6.67
General disorders and administration site conditions	4	4	12.5	2	2	6.67
Hepatobiliary disorders	0	0	0	2	1	3.33
Immune system disorders	1	1	3.13	0	0	0
Infections and infestations	7	7	21.88	10	9	30
Investigations	3	3	9.38	4	4	13.33
Metabolism and nutrition disorders	2	2	6.25	2	2	6.67
Musculoskeletal and connective tissue disorders	2	2	6.25	2	2	6.67
Nervous system disorders	23	14	43.75	9	8	26.67
Pregnancy, puerperium and perinatal conditions	0	0	0	1	1	3.33
Psychiatric disorders	11	7	21.88	4	4	13.33
Renal and urinary disorders	4	2	6.25	1	1	3.33
Respiratory, thoracic and mediastinal disorders	1	1	3.13	0	0	0
Skin and subcutaneous tissue disorders	3	3	9.38	2	2	6.67
Vascular disorders	0	0	0	1	1	3.33

Table 50: Treatment-Emergent Adverse Events Occurring in > 2% of Pitolisant Patients and More Frequently than Placebo – HARMONY I (P07-03)

Adverse Events	Pitolisant (N=31)	%	Modafinil (N=33)	%	Placebo (N=30)	%
Headache	12	38.7%	7	21.2%	6	20.0%
Rash, eruption, dermatitis	3	9.6%	0	0.0%	0	0.0%
Insomnia, poor quality sleep	3	9.6%	0	0.0%	0	0.0%
Abdominal pain	3	9.6%	6	18.1%	0	0.0%
Upper Respiratory Infection	2	6.5%	3	9.0%	1	3.3%
Tachycardia	2	6.5%	2	6.0%	0	0.0%
Somnolence, sedation	2	6.5%	0	0.0%	1	3.3%
Hallucinations	2	6.5%	0	0.0%	0	0.0%
Asthenia, fatigue, malaise, weakness	2	6.5%	0	0.0%	0	0.0%
Dysuria, pollakiuria, polyuria	2	6.5%	0	0.0%	0	0.0%
Aphthous ulcer, oral mucosal blistering, stomatitis	1	3.2%	0	0.0%	0	0.0%
Oropharyngeal pain	1	3.2%	0	0.0%	0	0.0%
Hyperhidrosis	1	3.2%	0	0.0%	0	0.0%
Hemorrhoids	1	3.2%	0	0.0%	0	0.0%
Dry eye	1	3.2%	0	0.0%	0	0.0%
Fever	1	3.2%	0	0.0%	0	0.0%
Respiratory distress	1	3.2%	0	0.0%	0	0.0%
Dyskinesia, tongue movement disturbance	1	3.2%	0	0.0%	0	0.0%
Anxiety, nervousness, panic attacks	1	3.2%	2	6.0%	0	0.0%
Irritability	1	3.2%	2	6.0%	0	0.0%
Tremor, shakiness, trembling	1	3.2%	1	3.0%	0	0.0%
Dizziness, light-headedness	1	3.2%	4	12.1%	0	0.0%
Diarrhea	1	3.2%	4	12.1%	0	0.0%
Dry mouth, dry lips, thirst	1	3.2%	2	6.0%	0	0.0%
Anorexia, decreased appetite	1	3.2%	1	3.0%	0	0.0%

HARMONY CTP (P11-05): Psychiatric Disorders and Nervous System Disorders were the most frequently reported SOCs for TEAEs in pitolisant-treated patients, although Nervous System Disorders were reported less frequently than in the placebo group in this trial (Table 51). The TEAEs that occurred most commonly and at a frequency greater than in the placebo group were headache, infection, tachycardia, anxiety, irritability, sleep disturbance, and nausea (Table 52).

Table 51: Treatment Emergent Adverse Events by System Organ Class - HARMONY CTP (P11-05)

	Pitolisant (N = 54)			Placebo (N = 51)		
SOC	**Events**	**Number of subjects**	**Proportion (%)**	**Events**	**Number of subjects**	**Proportion (%)**
Cardiac disorders	3	3	5.56	0	0	0
Gastrointestinal disorders	4	3	5.56	0	0	0
General disorders and administration site conditions	2	2	3.7	2	2	3.85
Hepatobiliary disorders	1	1	1.85	0	0	0
Infections and infestations	2	2	3.7	0	0	0
Injury, poisoning and procedural complications	0	0	0	1	1	1.92
Investigations	4	4	7.41	8	4	7.69
Nervous system disorders	6	6	11.11	15	11	21.15
Psychiatric disorders	18	8	14.81	5	4	7.69
Reproductive system and breast disorders	0	0	0	1	1	1.92
Respiratory, thoracic and mediastinal disorders	0	0	0	1	1	1.92
Vascular disorders	1	1	1.85	0	0	0

Table 52: Treatment-Emergent Adverse Events Occurring in > 2% of Pitolisant Patients and More Frequently than Placebo – HARMONY CTP (11-05)

Adverse Events	Pitolisant (N=54)	%	Placebo (N=51)	%
Headache	5	9.2%	6	11.5%
Infection (All)	3	5.6%	2	3.8%
Tachycardia	3	5.6%	0	0.0%
Anxiety, nervousness, panic attacks	3	5.6%	0	0.0%
Irritability	3	5.6%	1	1.9%
Sleep disturbance	3	5.6%	1	1.9%
Nausea	3	5.6%	0	0.0%
Upper Respiratory Infection	2	3.7%	1	1.9%
ECG abnormality (Twave inversion, Right bundle branch block)	3	3.7%	0	0.0%

HARMONY I-bis (09-15): Nervous System Disorders, Gastrointestinal Disorders, and Psychiatric Disorders were the most frequently reported SOCs for TEAEs in pitolisant-treated patients in HARMONY I-bis (Table 53). The TEAEs occurring most commonly and at a frequency greater than in the placebo group were headache, insomnia (including poor quality sleep), and musculoskeletal pain (for this analysis, musculoskeletal adverse events including myalgia,

arthralgia, limb discomfort, musculoskeletal pain, carpal tunnel syndrome, back pain, neck pain, and sciatica were pooled into a single adverse event category, Table 54).

Table 53: Treatment Emergent Adverse Events by System Organ Class - HARMONY I-bis (P09-15)

	Pitolisant (N = 67)			Placebo (N = 33)		
SOC	**Events**	**Number of subjects**	**Proportion (%)**	**Events**	**Number of subjects**	**Proportion (%)**
Cardiac disorders	1	1	1.49	0	0	0
Eye disorders	0	0	0	1	1	3.03
Gastrointestinal disorders	27	13	19.4	9	5	15.15
General disorders and administration site conditions	6	4	5.97	3	3	9.09
Infections and infestations	6	5	7.46	5	5	15.15
Injury, poisoning and procedural complications	2	1	1.49	0	0	0
Investigations	5	2	2.99	1	1	3.03
Metabolism and nutrition disorders	4	4	5.97	2	2	6.06
Musculoskeletal and connective tissue disorders	11	6	8.96	1	1	3.03
Nervous system disorders	40	21	31.34	15	8	24.24
Pregnancy, puerperium and perinatal conditions	1	1	1.49	0	0	0
Psychiatric disorders	19	10	14.93	6	4	12.12
Reproductive system and breast disorders	2	1	1.49	0	0	0
Respiratory, thoracic and mediastinal disorders	1	1	1.49	0	0	0

Table 54: Treatment-Emergent Adverse Events Occurring in > 2% of Pitolisant Patients and More Frequently than Placebo – HARMONY I-bis (09-15)

Adverse Events	Pitolisant (N=67)	%	Modafinil (N=65)	%	Placebo (N=33)	%
Headache	11	16.4%	6	9.2%	5	15.1%
Insomnia, poor quality sleep	5	7.5%	1	1.5%	2	6.0%
Musculoskeletal pain	5	7.5%	5	7.7%	0	0.0%
Upper respiratory infection	4	5.8%	7	10.8%	1	3.0%
Dizziness, light-headedness	4	5.8%	1	1.5%	1	3.0%
Nausea	4	5.8%	1	1.5%	1	3.0%
Anxiety, nervousness, panic attacks	3	4.5%	2	3.1%	1	3.0%
Cataplexy	3	4.5%	2	3.1%	0	0.0%
Vomiting	3	4.5%	0	0.0%	0	0.0%
Anorexia, decreased appetite	3	4.5%	0	0.0%	0	0.0%
Somnolence, sedation	2	2.9%	3	4.6%	0	0.0%
Hallucinations	2	2.9%	1	1.5%	0	0.0%

*Musculoskeletal pain includes: myalgia, arthralgia, limb discomfort, musculoskeletal pain, carpal tunnel syndrome, back pain, neck pain, sciatica

Pooled Data – HARMONY I, HARMONY CTP, HARMONY I-bis: This review examined pooled adverse event data from HARMONY I, HARMONY CTP, and HARMONY I-bis. Table 55 shows a summary of the raw numbers of TEAEs that occurred in ≥2% of pitolisant-treated patients and more frequently in the placebo group. While the trial designs of HARMONY I and HARMONY I-bis were similar, patients in HARMONY I were randomized 1:1:1 to receive either pitolisant, modafinil, or placebo, but patients in HARMONY I-bis were randomized 2:2:1 to these treatment groups. The randomization ratio in HARMONY CTP, which included only pitolisant and placebo arms, was 1:1. Therefore, the percentage of participants with TEAEs in each study was also weighted to account for differences in the randomization ratios in the trials (Table 56). The modafinil arms in HARMONY I and HARMONY I-bis were also excluded from the analysis. The weighted total was calculated as follows:

A = Proportion of pitolisant-treated subjects with a given AE (P0703) x total number of non-modafinil-treated subjects (N=31)
B = Proportion of pitolisant-treated subjects with a given AE (P0915) x total number of non-modafinil-treated subjects (N=67)
C = Proportion of pitolisant-treated subjects with a given AE (P1105) x total number of non-modafinil-treated subjects (N=54)
D = Total Number of pitolisant-treated and placebo-treated subjects in P0703, P0915, P1105

(A+B+C)/D = Weighted total for a given adverse event

A similar calculation was performed for the placebo group.

The TEAEs occurring most frequently in pitolisant-treated patients and at a frequency greater than in the placebo group were headache, sleep disorder (including insomnia and poor-quality sleep), and nausea. Nervous System Disorders, Psychiatric Disorders, and Gastrointestinal Disorders were the most frequently reported SOCs for TEAEs (Table 57). The calculated percentages in the unweighted and weighted analyses for each adverse event were similar.

Table 55: Adverse Events Reported in > 2% of Pitolisant Patients and Occurring More Frequently than in Placebo – HARMONY I, HARMONY CTP, and HARMONY I-bis (Unweighted)

Adverse Events	Pitolisant (N=152)	%	Placebo (N=114)	%
Headache	28	18.4%	17	14.9%
Insomnia, poor quality sleep	9	5.9%	2	1.8%
Nausea	9	5.9%	3	2.6%
Upper Respiratory Tract Infection	8	5.3%	3	2.6%
Musculoskeletal pain*	7	4.6%	3	2.6%
Anxiety, nervousness, panic attacks	7	4.6%	1	0.9%
Tachycardia, heart rate increased	5	3.3%	0	0.0%
Hallucinations	5	3.3%	0	0.0%
Irritability	5	3.3%	2	1.8%
Dizziness, light-headedness	5	3.3%	3	2.6%
Abdominal pain	5	3.3%	1	0.9%
Anorexia, decreased appetite	4	2.6%	0	0.0%
Sleep disturbance	4	2.6%	2	1.8%
Cataplexy	3	2%	1	0.9%
Dry Mouth	3	2%	1	0.9%
Rash*	3	2%	1	0.9%

*Musculoskeletal pain includes: myalgia, arthralgia, limb discomfort, musculoskeletal pain, carpal tunnel syndrome, back pain, neck pain, sciatica
*Rash includes: eczema, erythema migrans, rash, urticaria

Table 56: Adverse Events Reported in ≥ 2% of Patients and Occurring More Frequently than in Placebo - HARMONY I, HARMONY CTP, and HARMONY I-bis (Weighted)

Adverse Events	Pitolisant (N=152)	%	Placebo (N=114)	%
Headache	49.8	18.7%	39.7	14.9%
Nausea	15.7	5.9%	7.1	2.7%
Insomnia, poor quality sleep	15.3	5.8%	6.1	2.3%
Upper Respiratory Infection	13.8	5.2%	7.1	2.7%
Anxiety, nervousness, panic attacks	12.3	4.6%	3.0	1.1%
Musculoskeletal pain	11.4	4.3%	6.1	2.3%
Tachycardia, heart rate increased	9.8	3.7%	0.0	0.0%
Irritability	9.3	3.5%	5.1	1.9%
Abdominal pain	8.9	3.3%	3.0	1.1%
Hallucinations	8.9	3.3%	0.0	0.0%
Dizziness, light-headedness	7.9	3.0%	7.1	2.7%
Sleep disturbance	7.3	2.8%	4.1	1.5%
Anorexia, decreased appetite	6.4	2.4%	0.0	0.0%
Rash	5.9	2.2%	2.0	0.8%
Dry mouth	5.0	1.9%	3.0	1.1%
Cataplexy	4.5	1.7%	2.0	0.8%

*Musculoskeletal pain includes: myalgia, arthralgia, limb discomfort, musculoskeletal pain, carpal tunnel syndrome, back pain, neck pain, sciatica

*Rash includes: eczema, erythema migrans, rash, urticaria

Table 57: Adverse Events Reported in > 2% of Pitolisant Patients and More Frequently than in Placebo by System Organ Class (SOC) - HARMONY I, HARMONY CTP, HARMONY I-bis (Unweighted)

	Pitolisant (N = 152)			Placebo (N = 114)		
SOC	**Events**	**Number of subjects**	**Proportion (%)**	**Events**	**Number of subjects**	**Proportion (%)**
Cardiac disorders	6	6	3.92	0	0	0
Eye disorders	1	1	0.65	1	1	0.87
Gastrointestinal disorders	43	22	14.38	11	7	6.09
General disorders and administration site conditions	12	10	6.54	7	7	6.09
Hepatobiliary disorders	1	1	0.65	2	1	0.87
Immune system disorders	1	1	0.65	0	0	0
Infections and infestations	15	14	9.15	15	14	12.17
Injury, poisoning and procedural complications	2	1	0.65	1	1	0.87
Investigations	12	9	5.88	13	9	7.83
Metabolism and nutrition disorders	6	6	3.92	4	4	3.48
Musculoskeletal and connective tissue disorders	13	8	5.23	3	3	2.61
Nervous system disorders	69	41	26.8	39	27	23.48
Pregnancy, puerperium and perinatal conditions	1	1	0.65	1	1	0.87
Psychiatric disorders	48	25	16.34	15	12	10.43
Renal and urinary disorders	4	2	1.31	1	1	0.87
Reproductive system and breast disorders	2	1	0.65	1	1	0.87
Respiratory, thoracic and mediastinal disorders	2	2	1.31	1	1	0.87
Skin and subcutaneous tissue disorders	3	3	1.96	2	2	1.74
Vascular disorders	1	1	0.65	1	1	0.87

HARMONY IV (P10-01): The most common TEAE reported in this study was headache, which occurred in 23% of pitolisant-treated patients and 10% of placebo-treated patients (Table 58). One participant in each treatment group reported a TEAE of insomnia. One patient in the placebo group experienced an adverse event of hypertension. No other psychiatric or cardiovascular adverse events were reported by any participant.

Table 58: Adverse Events Reported in ≥ 2% of Patients and Occurring More Frequently than Placebo - HARMONY IV (P10-01)

Adverse Event	Pitolisant (N=26)	%	Placebo (N=21)	%
Headache	6	23.1%	2	9.5%
Infection, all	5	19.2%	3	14.3%
Musculoskeletal pain	3	11.5%	2	9.5%
Abdominal Pain	3	11.5%	2	9.5%

*Musculoskeletal pain includes: myalgia, arthralgia, limb discomfort, musculoskeletal pain, carpal tunnel syndrome, back pain, neck pain, sciatica

HARMONY III (P09-10): The most common TEAEs in the open-label, long-term safety study were headache, increased weight, sleep disorders (including insomnia, dyssomnia, and sleep fragmentation), depression, anxiety, and nausea. TEAEs in the Psychiatric Disorders, Nervous System Disorders, Gastrointestinal Disorders, and Infections and Infestations SOC categories were reported most frequently in the study (Table 59).

Six patients in HARMONY III reported cardiac disorders, vascular disorders, and investigations related to cardiovascular events including: hypertension, hypotension, bradycardia, prolonged QT interval, nonspecific polarization abnormality, pericarditis, unspecified ECG change, and atrial fibrillation (one adverse event report each).

23 patients in HARMONY III reported psychiatric adverse events (excluding sleep-related events) including: depression (ten reports), anxiety (nine reports), irritability (four reports), hallucinations (three reports), agitation (two reports), mood disorder (one report), non-epileptiform seizure (one report), and suicidal ideation (one report). The single report of suicidal ideation occurred in patient [redacted] (b) (6) (case narrative summarized under SAEs in Section 8.4.2).

Table 59: Treatment Emergent Adverse Events in Open-label, Long-term Safety Study - HARMONY III (P0910)

	Pitolisant (N = 101)		
SOC	Events	Number of subjects	Proportion (%)
Blood and lymphatic system disorders	1	1	1%
Cardiac disorders	4	3	3%
Ear and labyrinth disorders	8	5	5%
Endocrine disorders	2	1	1%
Eye disorders	6	4	4%
Gastrointestinal disorders	47	23	22.8%
General disorders and administration site conditions	8	6	6%
Hepatobiliary disorders	1	1	1%
Infections and infestations	38	23	22.8%
Injury, poisoning and procedural complications	8	5	5%
Investigations	31	19	18.8%
Metabolism and nutrition disorders	8	7	6.9%
Musculoskeletal and connective tissue disorders	9	7	6.9%
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	1	1	1%
Nervous system disorders	38	24	23.8%
Pregnancy, puerperium and perinatal conditions	6	3	3%
Psychiatric disorders	56	34	33.7%
Renal and urinary disorders	1	1	1%
Reproductive system and breast disorders	5	5	5%
Respiratory, thoracic and mediastinal disorders	6	5	5%
Skin and subcutaneous tissue disorders	5	5	5%
Surgical and medical procedures	9	8	7.9%
Vascular disorders	5	4	4%

Relationship of Dose to Adverse Events: Table 60, Table 61, and Table 62 present adverse events by assigned dosing group in HARMONY I, HARMONY CTP, and HARMONY I-bis. These trials included patients who received low dose pitolisant (5 mg to 10mg), medium dose pitolisant (20 mg), and high dose (40 mg). The higher dose (40 mg) was not clearly associated with higher frequency of adverse events. However, this analysis is limited by the small number of patients in each dosing group. Furthermore, this analysis considered only the assigned dosing group and not the actual dose taken by the patient at the time of the adverse event.

Table 60: Adverse Events by Dose Group - HARMONY I (P07-03)

Adverse Event	Low dose (5 to 10 mg) N=2	%	Medium dose (20 mg) N=10	%	High dose (40 mg) N=19	%
Headache	1	50%	3	30%	8	42%
Not categorized	0	0%	0	0%	2	10.5%
Tachycardia	0	0%	0	0%	2	10.5%
Abdominal pain	1	50%	0	0%	2	10.5%
Infection, all	1	50%	1	10%	2	10.5%
Rash, eruption, dermatitis	0	0%	1	10%	2	10.5%
Hyperhidrosis	0	0%	0	0%	1	5.3%
Hemorrhoids	0	0%	0	0%	1	5.3%
Dry eye	0	0%	0	0%	1	5.3%
Urinary tract infection	0	0%	0	0%	1	5.3%
Eczema	0	0%	0	0%	1	5.3%
Respiratory distress	0	0%	0	0%	1	5.3%
Musculoskeletal Disorders	1	50%	0	0%	1	5.3%
Dyskinesia, tongue movement disturbance	0	0%	0	0%	1	5.3%
Psychosis, delusions, hallucinations	1	50%	0	0%	1	5.3%
Tremor, shakiness, trembling	0	0%	0	0%	1	5.3%
Insomnia, poor quality sleep	2	100%	0	0%	1	5.3%
Dizziness, light-headedness	0	0%	0	0%	1	5.3%
Asthenia, fatigue, malaise, weakness	1	50%	0	0%	1	5.3%
Dysuria, pollakiuria, polyuria	0	0%	1	10%	1	5.3%
Nausea	0	0%	1	10%	1	5.3%
Dry mouth, dry lips, thirst	0	0%	0	0%	1	5.3%
Weight gain	0	0%	0	0%	1	5.3%
Aphthous Ulcer, Oral mucosal blistering, stomatitis	1	50%	0	0%	0	0%
Oropharyngeal pain	1	50%	0	0%	0	0%
Allergic reaction, hypersensitivity	0	0%	1	10%	0	0%
Fever	1	50%	0	0%	0	0%

Upper respiratory Infection	1	50%	1	10%	0	0%
Somnolence, sedation	1	50%	1	10%	0	0%
Depression	1	50%	0	0%	0	0%
Anxiety, nervousness, panic attacks	0	0%	1	10%	0	0%
Irritability	0	0%	1	10%	0	0%
Diarrhea	1	50%	0	0%	0	0%
Anorexia, decreased appetite	1	50%	0	0%	0	0%

Table 61: Adverse Events by Dose Group - HARMONY CTP (P11-05)

Adverse Events	LOW (5 to 10 mg) N=8	%	MEDIUM (20 mg) N=11	%	HIGH (40 mg) N=35	%
Tachycardia	0	0%	1	9.1%	2	5.7%
Sleep disturbance	1	12.5%	0	0%	2	5.7%
Headache	2	25.0%	1	9.1%	2	5.7%
Infection, all	0	0%	2	18.2%	1	2.9%
Upper Respiratory Infection	0	0%	1	9.1%	1	2.9%
T-wave inversion	0	0%	0	0%	1	2.9%
Hypertension, BP increased	0	0%	0	0%	1	2.9%
Palpitations	0	0%	0	0%	1	2.9%
CPK increased	0	0%	0	0%	1	2.9%
Anxiety, nervousness, panic attacks	2	25.0%	0	0%	1	2.9%
Irritability	2	25.0%	0	0%	1	2.9%
Nausea	1	12.5%	1	9.1%	1	2.9%
Bundle branch block right	0	0%	1	9.1%	0	0%
Somnolence, sedation	1	12.5%	0	0%	0	0%
Depression	1	12.5%	0	0%	0	0%
Psychosis, delusions, hallucinations	0	0%	1	9.1%	0	0%
Insomnia, poor quality sleep	1	12.5%	0	0%	0	0%
Asthenia, fatigue, malaise, weakness	2	25.0%	0	0%	0	0%

Table 62: Adverse Events by Dose Group - HARMONY I-bis (P09-15)

Adverse Events	LOW DOSE (5 TO 10 mg) N=22	%	MEDIUM DOSE (20 mg) N=45	%
Headache	3	13.6 %	7	15.6 %
Musculoskeletal disorders	1	4.5%	3	6.7%
Nausea	1	4.5%	3	6.7%
Vomiting	0	0%	3	6.7%
Anorexia, decreased appetite	1	4.5%	2	4.4%
Infection, all	2	9.1%	2	4.4%
Not categorized	1	4.5%	1	2.2%
Meningitis	0	0%	1	2.2%
Upper respiratory infection	2	9.1%	1	2.2%
Angina	0	0%	1	2.2%
Psychosis, delusions, hallucinations	0	0%	1	2.2%
Anxiety, nervousness, panic attacks	0	0%	1	2.2%
Tremor, shakiness, trembling	0	0%	1	2.2%
Dizziness, light-headedness	3	13.6 %	1	2.2%
Asthenia, fatigue, malaise, weakness	0	0%	1	2.2%
Dyspepsia	0	0%	1	2.2%
Dry mouth, dry lips, thirst	1	4.5%	1	2.2%
Aphthous Ulcer, oral mucosal blistering, stomatitis	1	4.5%	0	0%
Oropharyngeal pain	1	4.5%	0	0%
Fluid retention	1	4.5%	0	0%
Dysmenorrhea	1	4.5%	0	0%
Fever	1	4.5%	0	0%
CPK increased	1	4.5%	0	0%
Heart rate irregular	1	4.5%	0	0%
Somnolence, sedation	1	4.5%	0	0%
Depression	1	4.5%	0	0%
Akathisia, restlessness	1	4.5%	0	0%
Agitation	1	4.5%	0	0%
Irritability	1	4.5%	0	0%
Insomnia, poor quality sleep	4	18.2 %	0	0%
Sleep disturbance	1	4.5%	0	0%
Abnormal dreams, nightmares	1	4.5%	0	0%

Cataplexy	1	4.5%	0	0%
Elevated GFT, LFTs	1	4.5%	0	0%
Diarrhea	2	9.1%	0	0%
Abdominal pain	1	4.5%	0	0%

Reviewer Comment: The most common adverse event reported in HARMONY I, HARMONY CTP, and HARMONY I-bis was headache. While narcolepsy is associated with excessive daytime sleepiness, sleep fragmentation and poor-quality nighttime sleep also occur commonly. In these trials, patients in the pitolisant group reported symptoms of insomnia and poor-quality sleep more often than patients in the placebo group. Psychiatric conditions are also frequently co-morbid with narcolepsy, but patients in the pitolisant group reported more non-sleep-related psychiatric adverse events (depression, anxiety, hallucinations, agitation, irritability) than patients in the placebo group. Pitolisant also appeared to be associated with gastrointestinal adverse events such as nausea and abdominal pain. Psychiatric disorders, Nervous System Disorders, and Gastrointestinal disorders were the most common categories of TEAEs in the open-label, long-term safety study as well; no unexpected safety signals appeared to arise from chronic use. Higher doses of pitolisant were not clearly associated with risk of adverse events.

8.4.6. Laboratory Findings

This review analyzed laboratory findings from HARMONY I, HARMONY CTP, and HARMONY I-bis. The laboratory parameters assessed in the clinical trials included chemistries, lipids, complete blood count, and tests of coagulation. Table 63 and Table 64 list the reference ranges for all laboratory parameters. The pitolisant and placebo groups had comparable baseline laboratory values and the mean changes in laboratory parameters after treatment were similar in the pitolisant group as compared to the placebo group. Please refer to Table 6, Table 15, and Table 21 for the schedule of assessments in each trial.

Table 63: Standard Normal Ranges for Hematological Tests

Hematology Laboratory Test	Unit	Normal Range
Hemoglobin	g/L	Female: 123 - 157; Male: 130 – 170
Hematocrit	%	Female: 37 - 46; Male: 38 – 50
Platelets	$x\ 10^9/L$	110 – 450
RBC	$x\ 10^9/L$	4 - 6.2
WBC	$x\ 10^9/L$	3.5 – 11
Neutrophil, Absolute	$x\ 10^9/L$	1.6 - 6.6
Lymphocytes, Absolute	$x\ 10^9/L$	1.5 - 3.5
Monocytes, Absolute	$x\ 10^9/L$	0.2 - 1.1
Eosinophils, Absolute	$x\ 10^9/L$	0 – 5
Basophils, Absolute	$x\ 10^9/L$	0 – 3

Abbreviations: RBC: red blood cell; WBC: white blood cell
Source: Applicant ISS reviewer's guide, pages 18-19

Table 64: Standard Normal Ranges for Serum Chemistry and Coagulation Tests

Serum Chemistry or Coagulation Laboratory Test	Units	Normal Range
Sodium	mmol/L	135 – 145
Potassium	mmol/L	3.4 - 5.0
Chloride	mmol/L	95 – 110
Calcium	mmol/L	2.18 - 2.58
BUN	mmol/L	2.5 - 8.0
Bilirubin	µmol/L	<=26
Alkaline Phosphatase	units/L	23 – 115
AST	units/L	5.0 – 50
ALT	units/L	5.0 – 40
Creatinine	µmol/L	Female: 50 -90; Male: 70 -120
Glucose	mmol/L	3.3 - 5.8
Cholesterol	mmol/L	<5.2
GGT	units/L	Female: 5 - 36; Male: 8 – 61
Prothrombin Ratio		0.9 - 1.2
Triglycerides	mmol/L	<2.2
Total Protein	g/L	60 – 80

Factor V	%	70 – 165
MCV	fL	80 – 100
MCH	pg	27 – 33
MCHC	g/L	310 – 370
RDW	%	11.5 - 14.5

Abbreviations: ALT: alanine aminotransferase; AST: aspartate aminotransferase; BUN: blood urea nitrogen; GGT: gamma-glutamyltransferase; MCH: mean corpuscular hemoglobin; MCHC: mean corpuscular hemoglobin concentration; MCV: mean corpuscular volume; RDW: red blood cell distribution width
Source: Applicant ISS reviewer's guide, page 19

Treatment Emergent Adverse Events in the Investigations System Organ Class: Two patients in the pitolisant group and five patients in the placebo group reported TEAEs in the Investigations SOC.

TEAEs in the Investigations SOC experienced by patients in the pitolisant group were as follows:

- (b) (6): Creatine Phosphokinase (CPK), AST, ALT, and GGT increased
- (b) (6): CPK increased

TEAEs in the Investigations SOC experienced by patients in the placebo group were as follows:

- (b) (6): Blood triglycerides increased
- (b) (6): White blood cell count, absolute neutrophil count, and monocyte count increased
- (b) (6): Blood glucose increased
- (b) (6): GGT increased
- (b) (6): Blood cholesterol increased

Hematology: No significant changes in hematology laboratory parameters were observed in either the pitolisant or placebo groups in HARMONY I, HARMONY CTP, or HARMONY I-bis (Table 65). The proportion of patients with out-of-range hematology values was comparable in the pitolisant and placebo groups.

Two patients in the pitolisant group had an absolute neutrophil count (ANC) below 1500 during the trials. In both cases, the baseline neutrophil count was also below the normal range. Both patients completed the study and neither patient reported any TEAEs. No patients in the placebo group had an ANC below 1500.

- (b) (6): baseline ANC of 1.41 and an ANC of 1.56 recorded during HARMONY CTP
- (b) (6): baseline ANC of 2.76 and an ANC of 1.02 recorded during HARMONY CTP

Table 65: Mean Changes in Hematology Laboratory Assessments- HARMONY I, HARMONY CTP, HARMONY I-bis

Laboratory Parameter	Pitolisant		Placebo	
	Baseline	Mean Change	Baseline	Mean Change
Leukocytes (x 10^9/L)	7.2	-0.1	7.3	-0.3
Neutrophils (x 10^9/L)	4.4	-0.3	4.7	-0.2
Lymphocytes (x 10^9/L)	2.1	0.1	2.1	-0.1
Monocytes (x 10^9/L)	0.5	-0.01	0.5	-
Eosinophils (x 10^9/L)	0.2	-	0.2	-
Basophils (x 10^9/L)	0.04	-	0.04	-
Erythrocytes (x 10^9/L)	4.7	-	4.8	-0.1
Hemoglobin (g/L)	140	-0.2	143	-3.6
Hematocrit (%)	41.6	0.3	42.3	-0.7
Platelets (x 10^9/L)	260	-2.2	260	-7.4

Serum Chemistry and Tests of Coagulation: No significant changes in serum electrolytes, renal function panels (BUN and creatinine), lipid panel (cholesterol, triglycerides), or tests of coagulation were noted in HARMONY I, HARMONY CTP, and HARMONY I-bis (Table 66). Overall, the proportion of patients with out-of-range values was similar in the pitolisant and placebo groups, though patients in the pitolisant group were somewhat more likely to have on-treatment sodium levels > 145 mmol/L and on-treatment potassium values of > 5.

Table 66: Mean Changes in Chemistry, Lipid Panel, and Coagulation Assessments – HARMONY I, HARMONY CTP, HARMONY I-bis

Parameter	Pitolisant		Placebo	
	Baseline	Mean Change	Baseline	Mean Change
Sodium (mmol/L)	141	-0.8	141	-0.3
Potassium (mmol/L)	4.5	-	4.5	0.8
Chloride (mmol/L)	104	-0.4	103	0.5
Calcium (mmol/L)	2.3	-	2.4	-0.1
Blood Urea Nitrogen (mmol/L)	5	-	5	-
Creatinine (µmol/L)	77	0.6	79	-0.2
Cholesterol (mmol/L)	5	-0.1	5	-0.2
Triglycerides (mmol/L)	1.4	-	1.8	-
GGT	35.2	-1.7	35.5	0.84
ALT	26.0	-0.9	26.5	1.7
AST	21.9	-0.4	22.7	1.4
Alkaline phosphatase	106.2	-5.5	101.2	-3.6
Total Bilirubin	9.0	-0.1	9.4	-1.0
PTT ratio (INR)	1	-	1	-
Factor V (%)	105	-3.1	100	-0.7

Cholesterol and triglycerides were not assessed in HARMONY I.

Four patients in the placebo group and four patients in the pitolisant group had recorded serum potassium levels of > 6 mmol/L during treatment, which, if accurate, could lead to clinically significant adverse effects. The four patients in the pitolisant group with this finding are described below:

- (b) (6): This patient had a potassium of 3.74 mmol/L at baseline and a recorded potassium of 6.46 mmol/L during the premature drop-out visit. No other potassium levels are recorded for this patient. No on-treatment ECG is recorded for this patient; ECG was reportedly performed but not recorded. The patient experienced adverse events of pollakiuria and allergy to metals. The patient discontinued pitolisant because of perceived lack of efficacy.

- (b) (6): This patient had a baseline potassium of 4.36 mmol/L and a recorded potassium of 7.46 mmol/L at Visit 6. No end of study potassium value was obtained. The patient did not report any adverse events and completed the trial. On-treatment ECGs were unremarkable. This patient completed the study.

- (b) (6): This patient had a baseline potassium of 4.2 mmol/L, a recorded potassium of 6.43 mmol/L at Visit 6, and a recorded potassium of 2.09 mmol/L at Visit 7 (end of study visit). The patient reported adverse events of hypertension, upper

respiratory tract infection, increased heart rate, and dyssomnia during the trial. On-treatment ECGs were unremarkable. This patient completed the study.

- [redacted]: This patient had a baseline potassium of 8 mmol/L, a recorded potassium of 7.72 mmol/L at Visit 6, and a recorded potassium of 9.14 mmol/L at Visit 7 (end of study visit). PR interval on baseline ECG was 200 msec (borderline). On-treatment ECGs indicated a prolonged PR interval (maximum 220 msec). The patient completed the study and did not report any adverse events.

Reviewer comment: *The clinical details provided about these patients are not consistent with severe hyperkalemia and I suspect these values were the result of laboratory error or hemolyzed samples. Overall, the data do not suggest a consistent pattern of electrolyte disturbance with pitolisant treatment.*

Three patients in the pitolisant group and two patients in the placebo group had blood glucose values during treatment of < 2.8 mmol/L (approximately 50 mg/dl), which could be clinically significant. The patients in the pitolisant group with this finding are described below:

- [redacted]: This patient had a recorded serum glucose of 1.0 mmol/L recorded in HARMONY I-bis. The patient also experienced adverse events of depression and anxiety and chose to withdraw from the study for personal reasons. No other adverse events were reported.

- [redacted]: This patient had a recorded serum glucose of 1.3 mmol/L in HARMONY I as well as ALT greater than 3X the upper limit of normal. The patient also reported adverse events of rash and headache of moderate severity. The patient withdrew from the trial because of perceived lack of efficacy.

- [redacted]: The patient had a recorded serum glucose of 2.2 mmol/L in HARMONY CTP. The patient did not report any adverse events. The patient completed the study.

Reviewer comment: *The clinical significance of these findings is unclear as patients did not appear to report symptoms consistent with marked hypoglycemia.*

Tests of Liver Function: No patients in either the pitolisant or placebo group met Hy's law criteria for drug induced liver injury in the clinical trials. A similar proportion of patients in the pitolisant and placebo groups had liver function tests outside of the normal range (Table 67). As noted above, one patient ([redacted]) in the pitolisant group had TEAE's of elevated liver transaminases and GGT. This patient also reported TEAEs of nausea, diarrhea, increased CPK,

and cataplexy. Cataplexy was reported to be severe; other adverse events were mild or moderate in intensity. The patient completed the study (HARMONY I-bis). Another patient (b) (6)) in the pitolisant group had ALT elevation to 3X the upper limit of normal during HARMONY I. As described above, this patient, who withdrew from the trial, also experienced rash, headache, and a recorded serum glucose below 2.8 mmol/L.

Table 67: Patients with Liver Function Tests Outside of the Normal Range – HARMONY I, HARMONY CTP, HARMONY I-bis

Parameter (Units)	Pitolisant	% Pitolisant	Placebo	% Placebo	Reference Range
ALT (U/L)	20/152	13.1%	20/114	17.5%	5 to 40 U/L
AST (U/L)	5/152	3.3%	6/114	5.2%	5 to 50 U/L
Alkaline Phosphatase (U/L)	48/152	31.6%	40/114	35.1%	23 to 115 U/L
Bilirubin, Total (µmol/L)	2/152	1.3%	0/114	0%	≤ 26 µmol/L

Reviewer comment: Overall, no pattern of change suggestive of a drug-treatment effect was noted in any laboratory parameter.

8.4.7. Vital Signs

Weight: The mean change in weight over the 8-week treatment phase in HARMONY I and HARMONY I-bis and the 7-week treatment phase in HARMONY CTP did not differ significantly in the pitolisant, modafinil, and placebo groups (Table 68). However, four patients in the pitolisant group did experience significant weight gain of > 10 kg during the treatment phase, though none of these patients reported weight-related concerns as TEAEs. None of these patients experienced clinically significant elevations of serum glucose or liver transaminases. Two of these patients experienced elevations in triglycerides and cholesterol; the other two patients did not have any recorded assessments of triglycerides or cholesterol.

One patient in the pitolisant group (who did not experience weight gain > 10 kg) reported weight gain as a TEAE. No patients in the placebo group experienced weight gain or weight loss > 10 kg, though two patients in the placebo group reported weight gain as a TEAE. Four patients in the pitolisant group and one patient in the modafinil group reported anorexia or loss of appetite, while no patients in the placebo group reported this concern. No patients in the pitolisant or placebo groups reported weight loss as a TEAE (compared with one patient in the modafinil group).

Table 68: Changes in Body Weight - HARMONY I, HARMONY CTP, HARMONY I-bis

Weight	Pitolisant	%	Modafinil	%	Placebo	%
Mean Change (kg)	0.5	-	-0.2	-	0.2	x
Weight Loss > 10 kg	1/152	0.7%	0	0%	0	0%
Weight Gain > 10 kg	4/152	2.6%	0	0%	0	0%

Systolic and Diastolic Blood Pressure: In HARMONY I, HARMONY CTP, and HARMONY I-bis, no significant differences in the mean systolic or diastolic blood pressures or the mean changes in systolic and diastolic blood pressures were observed. One patient in the pitolisant group, one patient in the placebo group, and two patients in the modafinil group reported a TEAE of hypertension. Hypotension was not reported as a TEAE in any of the treatment groups. A similar proportion of patients in the pitolisant group as compared to the placebo group had out of range blood pressure values (systolic blood pressure < 90 mmHg or > 140 mmHg or diastolic blood pressure < 60 mmHg or > 90 mmHg, Table 69 and Table 70). In these trials, pitolisant did not appear to differ significantly from modafinil, the active control, in effects on systolic or diastolic blood pressure.

Table 69: Systolic Blood Pressure Effects - HARMONY I, HARMONY CTP, HARMONY I-bis

Systolic Blood Pressure (mmHg)	Pitolisant	%	Modafinil	%	Placebo	%
Mean Systolic Blood Pressure, Baseline	122	-	122	-	123	-
Mean Systolic Blood Pressure, Treatment	122	-	122	-	122	-
Systolic Blood Pressure > 140 mmHg	24/152	16%	16/98	16%	16/114	14%
Systolic Blood Pressure < 90 mmHg	3/152	2%	1/98	1%	1/114	0.8%
Mean Change, Systolic Blood Pressure (mmHg)	-0.32	-	0.035	-	-1.044	-
Max Change, Systolic Blood Pressure (mmHg)	50	-	41	-	40	-
Change, Systolic Blood Pressure, 25%ile to 75%ile (mmHg)	-8 to 5	-	-7 to 7	-	-8 to 5	-
Systolic Blood Pressure Range (mmHg)	80 to 180	-	80 to 167	-	80 to 170	-

Table 70: Diastolic Blood Pressure Effects - HARMONY I, HARMONY CTP, HARMONY I-bis

Diastolic Blood Pressure (mmHg)	Pitolisant	%	Modafinil	%	Placebo	%
Mean Diastolic Blood Pressure, Baseline	78	-	78	-	78	-
Mean Diastolic Blood Pressure, Treatment	76	-	78	-	77	-
Diastolic Blood Pressure > 90 mmHg	18/152	12%	12/98	12%	15/114	13%
Diastolic Blood Pressure < 60 mmHg	7/152	5%	4/98	4%	4/114	4%
Mean Change, Diastolic Blood Pressure	-0.46	-	-0.45	-	-0.42	-
Max Change. Diastolic Blood Pressure	26	-	28	-	33	-
Change, Diastolic Blood Pressure, 25%ile to 75%ile (mmHg)	-5 to 5	-	-5 to 5	-	-5 to 5	-
Diastolic Blood Pressure Range	50 to 115	-	50 to 110	-	50 to 110	-

Heart rate: The mean heart rates were similar in all treatment groups in HARMONY I, HARMONY CTP, and HARMONY I-bis and a similar proportion of patients experienced tachycardia (defined as a heart rate of > 90 beats per minute) and bradycardia (defined as a heart rate of < 60 beats per minute). The mean change in heart rate in all treatment groups was small and unlikely to be clinically significant (Table 71). Five patients in the pitolisant group and two patients in the modafinil group reported tachycardia as a TEAE (compared to no patients in the placebo group). No patients in any treatment group reported bradycardia as a TEAE.

Table 71: Heart Rate Effects - HARMONY I, HARMONY CTP, HARMONY I-bis

Heart Rate (Beats per Minute)	Pitolisant	%	Modafinil	%	Placebo	%
Mean Heart Rate, Baseline (bpm)	71	-	70	-	71	-
Mean Heart Rate, Post Treatment (bpm)	71	-	72	-	72	-
Heart Rate > 90 beats per minute (bpm)	18/152	12%	11/98	11%	12/114	11%
Heart Rate < 60 beats per minute (bpm)	34/152	22%	29/98	30%	23/114	20%
Mean Change, Heart Rate (bpm)	0.98	-	2	-	0.77	-
Max Change, Heart Rate (bpm)	42	-	36	-	47	-
Change, Heart Rate, 25%ile to 75%ile (bpm)	-5 to 6	-	-5 to 8	-	-5 to 6	-

Reviewer comment: Patients in the pitolisant group were more likely to report significant weight gain, which was associated with metabolic changes in some cases. However, the mean change in weight in the pitolisant group was modest. Although patients in the pitolisant group were more likely to report tachycardia as a TEAE, the mean post-treatment heart rates, the mean change in heart rate, and the proportion of patients with measured tachycardia or bradycardia were similar in the pitolisant and placebo group. Overall, pitolisant appears to be relatively neutral in its effects on weight, blood pressure, and heart rate.

8.4.8. Electrocardiograms (ECGs)

Standard 12-lead ECGS were conducted according to the schedule outlined in Table 6, Table 15, and Table 21 in HARMONY I, HARMONY CTP, and HARMONY I-bis. I reviewed on-treatment mean values for QRS, PR, aggregate QT, QTcF, and QTcB as well as the mean changes for each of these parameters. In addition, I identified patients in each treatment group whose intervals fell outside of the normal range. Patients in the pitolisant, modafinil, and placebo groups had comparable baseline and on-treatment ECG parameters.

Table 72: ECG Parameters - HARMONY I, HARMONY CTP, HARMONY I-bis

	Pitolisant	Placebo
ECG Parameter		
PR interval		
Mean Baseline (msec)	159.2	160.2
Mean On-Treatment	163	156.7
Mean Change	4.28	-2.15
PR > 200 msec (%)	24%	22%
QRS		
Mean Baseline (msec)	90.3	91.2
Mean On-Treatment	89.7	91.1
Mean Change	-0.75	-0.26
QRS > 120 (%)	9.90%	6.70%
QTcB		
Mean Baseline (msec)	408.9	415.3
Mean On-Treatment	408.8	412.7
Mean Change	-0.1	-1
Maximum Change	151.9	102.4
QTcB > 450 (%)	13%	16.70%
QTcF		
Mean Baseline (msec)	399.8	405.2
Mean On-Treatment	400.4	402.4
Mean Change	-0.1	-2.2
Maximum Change	116	58
QTcF > 450 (%)	3%	5%

8.4.9. QT

The Sponsor evaluated the effect of pitolisant on the QT interval in two studies (Studies P09-11 and P14-05). The Division obtained consultation from the interdisciplinary QT-IRT team for

additional review of these studies. Please see the QT-IRT consult for full details of the review. Study P09-11 was a total QT (TQT) study that evaluated doses up to 120 mg (single dose). Study P14-05 was a single ascending dose (SAD) study that evaluated doses up to 240 mg. The TQT study did not find a clinically significant QTc prolonging effect with the recommended pitolisant dose of 40 mg once daily, though a dose of 120 mg was associated with QTc prolongation of approximately 10 milliseconds (msec).

The QT/IRT team provided the following comments:

"A concentration-dependent QTc prolongation over a dose range of 40 to 240 mg was detected in this QT assessment. At steady state concentrations with the 40 mg dose, the expected mean (90% CI) increase in QTc is 4.2 (3.2 to 5.2) msec. The high clinical exposure identified is when patients who are CYP2D6 poor metabolizers take pitolisant 40 mg/day. Under this scenario, the expected mean (90% CI) increase in QTc is 8.6 (6.7 to 10.5) msec. The highest dose tested (240 mg) provides a 1.8-fold exposure margin over the high clinical exposure scenario and the expected mean increase is 15.5 (12.0 o 18.9) msec."

Reviewer comment: Most patients who receive pitolisant are unlikely to reach exposures seen with the 240 mg dose, as the highest recommended dose is 40 mg once daily. However, patients with hepatic or renal insufficiency, patients who are taking concomitant medications that interfere with CYP2D6 metabolism, and patients who are poor metabolizers of CYP2D6 may experience higher exposures. In addition, any QT prolongation in patients with underlying QT prolongation prior to initiation of treatment could be clinically significant (of note, patients with pre-existing QT interval prolongations were generally excluded from clinical trials). Labeling should include guidance for dosage adjustments in these populations.

8.4.10. Immunogenicity

No immunogenicity information was submitted with this application. In the narcolepsy clinical trials, one patient reported an allergy to electrodes. No other Immune System Disorders were reported.

8.5. Analysis of Submission-Specific Safety Issues

8.5.1. Psychiatric Adverse Events (Excluding sleep-related events) and BDI-SF scores

Pitolisant-treated patients experienced non-sleep related adverse events more frequently than patients receiving placebo. Anxiety was the most commonly reported non-sleep-related psychiatric adverse event. Although hypnagogic and hypnopompic hallucinations can be associated with narcolepsy, in the narcolepsy clinical trials only patients treated with pitolisant reported hallucinations. Depression did not appear to occur more often in the pitolisant group than in the placebo group.

Table 73: Treatment-Emergent Psychiatric Adverse Events (Non-Sleep-Related) - HARMONY I (P07-03)

Psychiatric Adverse Event	Pitolisant (N=31)	%	Modafinil (N=33)	%	Placebo (N=30)	%
Hallucinations	2	6.5%	0	0%	0	0.0%
Depression	1	3.2%	1	3%	1	3.3%
Anxiety, nervousness, panic attacks	1	3.2%	2	6%	0	0.0%
Irritability	1	3.2%	2	6%	0	0.0%
Emotional mood disturbance (non-depressive)	0	0.0%	1	3%	1	3.3%
Abnormal behavior	0	0.0%	1	3%	0	0.0%
Agitation	0	0.0%	1	3%	0	0.0%
All Psychiatric Adverse Events	5	16.1%	8	24.20%	2	6.7%

Table 74: Treatment-Emergent Psychiatric Adverse Events (Non-Sleep-Related) - HARMONY CTP (P11-05)

Psychiatric Adverse Event	Pitolisant	%	Placebo	%
Anxiety, nervousness, panic attacks	3	5.6%	0	0.0%
Irritability	3	5.6%	1	1.9%
Depression	1	1.8%	2	3.9%
Hallucinations	1	1.8%	0	0.0%
Emotional mood disturbance (non-depressive)	0	0.0%	1	1.9%
All Psychiatric Adverse Events	8	14.8%	4	7.8%

Table 75: Treatment-Emergent Psychiatric Adverse Events (Non-Sleep-Related) - HARMONY I-bis (P09-15)

Psychiatric Adverse Event	Pitolisant (N=67)	%	Modafinil (N=65)	%	Placebo (N=33)	%
Anxiety, nervousness, panic attacks	3	4.4%	2	3.1%	1	3%
Depression	2	3.0%	1	1.5%	1	3%
Hallucinations	2	3.0%	1	1.5%	0	0%
Agitation	1	1.5%	1	3.1%	0	0%
Irritability	1	1.5%	1	3.1%	0	0%
Emotional Mood Disturbance (non-depressive)	0	0.0%	2	3.1%	0	0%
All Psychiatric Adverse Events	9	13.4 %	8	12.3 %	2	6.10%

Table 76: Treatment-Emergent Psychiatric Adverse Events - HARMONY I, HARMONY CTP, HARMONY I-bis (Weighted)

Psychiatric Adverse Event	Pitolisant (N=152)	%	Placebo (N=114)	%
Anxiety, nervousness, panic attacks	12.3	4.6%	3.0	1.1%
Irritability	9.3	3.4%	5.1	1.9%
Hallucinations	8.9	3.3%	0.0	0.0%
Depression	6.9	2.6%	11.2	4.2%
Agitation	1.5	0.5%	0.0	0.0%
Emotional mood disturbance (non-depressive)	0.0	0.0%	2.0	0.7%
All Psychiatric Adverse Events	38.8	14.6%	21.4	8.0%

Table 77: Treatment-Emergent Psychiatric Adverse Events – HARMONY I, HARMONY CTP, HARMONY I-bis (Unweighted)

Psychiatric Adverse Event	Pitolisant (N=152)	%	Placebo (N=114)	%
Anxiety, nervousness, panic attacks	7	4.6%	1	0.8%
Hallucinations	5	3.3%	0	0.0%
Irritability	5	3.3%	0	0.0%
Depression	4	2.6%	4	3.5%
Agitation	1	0.6%	0	0.0%
Emotional mood disturbance (non-depressive)	0	0.0%	2	1.8%
All Psychiatric Adverse Events	22	14.4%	7	6.1%

Mean BDI-SF scores were similar in all treatment groups in HARMONY I, HARMONY CTP, and HARMONY I-bis. BDI-SF decreased in all treatment groups by the end of treatment. In HARMONY I, mean BDI-SF scores were 4, 3, and 5 in the pitolisant, placebo, and modafinil groups, respectively. On the BDI-SF, scores between 0 and 4 indicate no depression or minimal depression and scores between 5 and 7 indicate mild depression. At the end of treatment, mean BDI-SF scores were 1.7, 1.3, and 2.8 in the pitolisant, placebo, and modafinil groups. In HARMONY CTP, mean BDI-SF scores were 5.3 and 5.4 in the pitolisant and placebo groups at baseline and 2.8 and 3.9 in the pitolisant and placebo groups at the end of treatment. In HARMONY I-bis, mean BDI-SF scores were 5, 5, and 4 in the pitolisant, placebo and modafinil groups. At the end of treatment, scores had decreased to 3.3, 3.4, and 2.5 in the pitolisant, placebo, and modafinil groups.

Two pitolisant-treated patients, three placebo-treated patients, and one modafinil-treated patient had BDI-SF Item G scores > 0 while on treatment. Item G on the BDI-SF assesses suicide risk.

Reviewer comment: No clear association with depression or suicide risk in pitolisant-treated patients was found in review of adverse event reports and BDI-SF scores. However, significant limitations related to the data provided by the BDI-SF were noted (e.g., BDI-SF was not required in protocols for all countries in P07-03 and Item G does not assess a full range of suicidal cognitions and behaviors). Patients who received pitolisant did report potentially distressing non-sleep-related psychiatric events more often than patients who received placebo, including anxiety and hallucinations. Information about the risk of psychiatric adverse events should be noted in labeling.

8.5.2. Cardiovascular Adverse Events

Pitolisant-treated patients were more likely to report cardiac disorders and vascular disorders than patients receiving placebo (Table 78). The absolute number of cardiovascular events was small. The most commonly reported adverse cardiovascular event was increased heart rate. However, as noted above, review of vital signs data did not reveal a meaningful difference in the heart rates of pitolisant-treated patients as compared to placebo-treated patients.

Table 78: Treatment-Emergent Cardiac Disorders, Vascular Disorders, and Investigations Related to Cardiovascular Events - HARMONY I, HARMONY CTP, HARMONY I-bis

Adverse Event	Pitolisant (N=152)	Modafinil (N=65)	Placebo (N=114)
Angina	1	0	0
Hypertension	1	2	1
Irregular heart rate	1	0	0
Palpitations	1	0	0
Right bundle branch block	1	0	0
Heart rate increased/tachycardia	5	2	0
Twave inversion	1	0	0
Total	11	4	1
%	7.2%	6.2%	0.9%

8.5.3. Seizures and Convulsions

No seizures or convulsions were reported in the narcolepsy clinical trials. One patient in a study evaluating the use of pitolisant for refractory partial seizures reported an SAE of increased frequency of seizures (Please see Section 8.4.2).

8.5.4. Withdrawal Symptoms and Indicators of Abuse Potential

The Applicant searched the ISS database (for all indications) for terms related to withdrawal and abuse potential. Their search included: terms in the standardized MedDRA query (SMQ) Drug Abuse and Dependence; terms with the MedDRA high level group term (HLGT) Mood Disorders and Disturbances not elsewhere classified (NEC); the MedDRA high level term (HLT) Substance-related disorders; and MedDRA preferred terms (PT) and lower level terms (LLT) that correspond to those outlined in the FDA guidance (https://www.fda.gov/media/116739/download). Table 71 (provided by the Applicant) summarizes the TEAEs potentially related to abuse potential. No patients who received pitolisant reported experiencing a drug withdrawal syndrome or euphoric mood. No overdoses were reported in the clinical development program.

Table 79: TEAEs with Possible Association with Abuse Potential in Narcolepsy Clinical Trials

MedDRA SOC Preferred Term	Double-Blind Placebo-Controlled			Single-Blind and Open-Label Pitolisant (N=137) n (%)	TOTAL Pitolisant (N=303) n (%)
	Modafinil (N=95) n (%)	Placebo (N=131) n (%)	Pitolisant (N=172) n (%)		
Any TEAE Indicative of Abuse Potential	15 (15.8)	12 (9.2)	18 (10.5)	9 (6.6)	27 (8.9)
General disorders and administration site conditions	**1 (1.1)**	**1 (0.8)**	**0**	**0**	**0**
Drug withdrawal syndrome	1 (1.1)	0	0	0	0
Feeling abnormal	0	1 (0.8)	0	0	0
Nervous system disorders	**7 (7.4)**	**7 (5.3)**	**9 (5.2)**	**3 (2.2)**	**12 (4.0)**
Dizziness	5 (5.3)	3 (2.3)	6 (3.5)	2 (1.5)	8 (2.6)
Somnolence	2 (2.1)	4 (3.1)	3 (1.7)	1 (0.7)	4 (1.3)
Psychiatric disorders	**7 (7.4)**	**5 (3.8)**	**10 (5.8)**	**6 (4.4)**	**16 (5.3)**
Affective disorder	1 (1.1)	1 (0.8)	0	1 (0.7)	1 (0.3)
Apathy	0	2 (1.5)	1 (0.6)	0	1 (0.3)
Disorientation	0	1 (0.8)	0	0	0
Dysphoria	1 (1.1)	0	1 (0.6)	0	1 (0.3)
Euphoric mood	1 (1.1)	0	0	0	0
Hallucination	1 (1.1)	0	3 (1.7)	0	3 (1.0)
Irritability	3 (3.2)	1 (0.8)	5 (2.9)	5 (3.6)	10 (3.3)
Mood altered	0	1 (0.8)	0	0	0

Source – Applicant's Integrated Summary of Safety, Table 52, page 127

CSS has performed a consultative review of the data related to human abuse liability potential (review completed by Dr. Katherine Bonson, PhD, Silvia Calderon PhD, and Wei Liu, PhD). Please see CSS consult for full details of the analysis. CSS determined that pitolisant has low abuse liability potential at recommended doses. Of note, the Amphetamine-like Withdrawal Questionnaire was administered to patients at the end of the study, during the 7-day withdrawal period (during which all patients received placebo). The CSS review notes that the questionnaire was only administered once or twice and that this administration was too long after the termination of treatment to accurately assess withdrawal symptoms. However, the CSS review concludes that "there were no AEs indicative of withdrawal in the first 7 or 30 days after pitolisant discontinuation. This suggests that pitolisant does not induce physical dependence."

Reviewer comment: *The low human abuse liability potential represents a significant safety advantage over other approved products for the treatment of narcolepsy.*

8.6. Safety Analyses by Demographic Subgroups

Gender: Male patients who received pitolisant in HARMONY I, HARMONY CTP, and HARMONY I-bis were more likely to report Psychiatric Disorders and Gastrointestinal Disorders (**Figure 17**). Female patients appeared to experience Nervous System Disorders (e.g., headache) more frequently than male patients (**Figure 18**).

Figure 17: Treatment Emergent Adverse Events in Male Pitolisant-Treated Patients

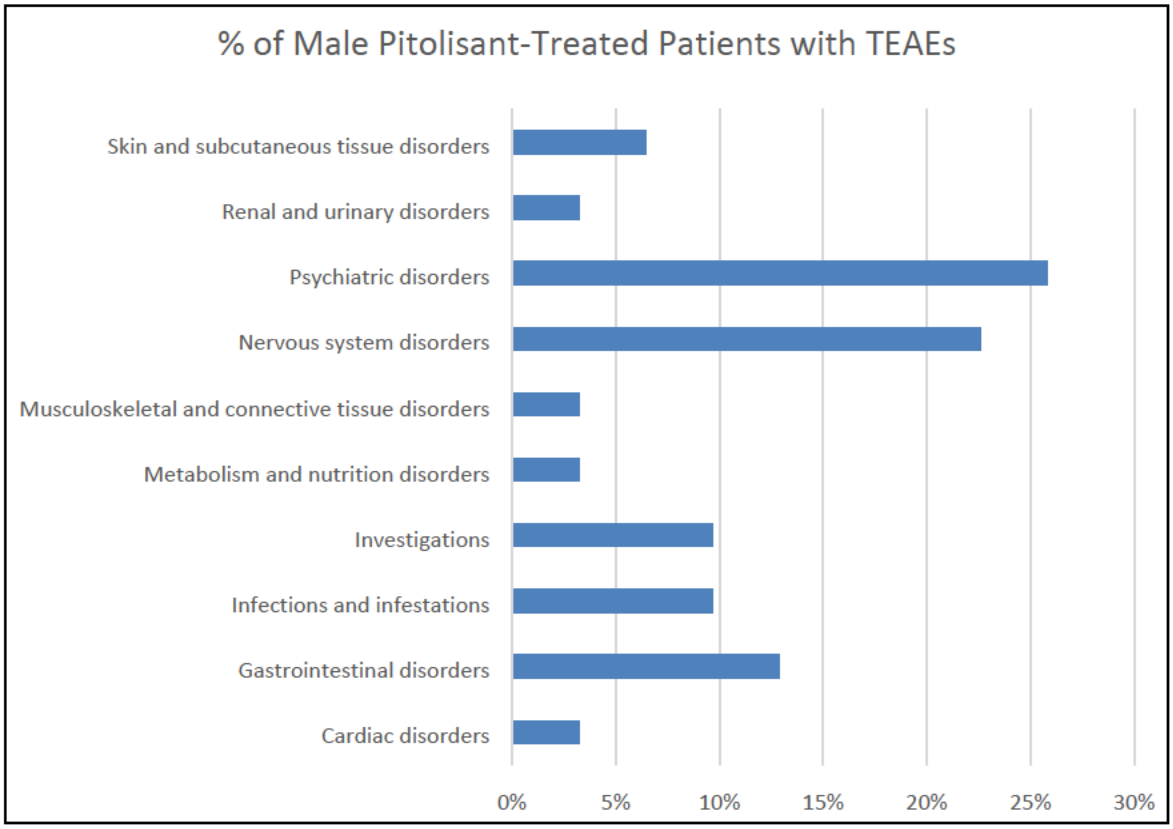
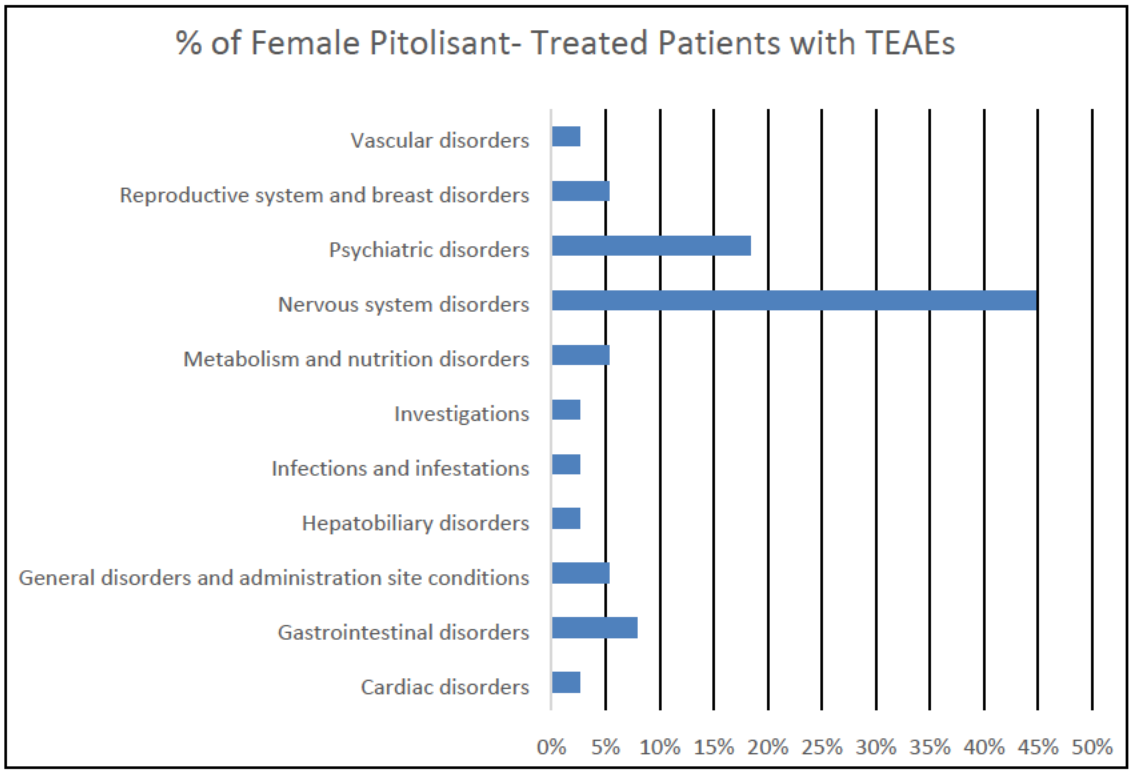


Figure 18: Treatment Emergent Adverse Events in Female Pitolisant-Treated Patients



Age: Patients ≥ 65 years of age accounted for approximately 5% of pitolisant treated patients in HARMONY I, HARMONY CTP, and HARMONY I-bis and approximately 3% of TEAEs.

Patients with cataplexy: The TEAEs in the cataplexy that occurred most frequently (and more often than placebo) were headache, insomnia, nausea, and upper respiratory infection. The adverse event profile in patients with cataplexy was comparable to the adverse event profile in the overall study population (**Table 80**).

Table 80: TEAEs in the Cataplexy Population Occurring in > 2% of Pitolisant Patients and More Frequently than Placebo – HARMONY I, HARMONY CTP, HARMONY I-bis

Adverse Event	Pitolisant	%	Placebo	%
Headache	24	18.6%	14	13.7%
Insomnia, poor quality sleep	10	7.8%	0	0.0%
Nausea	9	7.0%	2	2.0%
Upper Respiratory Infection	6	4.7%	4	3.9%
Tachycardia, increased heart rate	6	4.7%	0	0.0%
Musculoskeletal pain	6	4.7%	4	3.9%
Hallucinations	5	3.9%	0	0.0%
Irritability	5	3.9%	2	2.0%
Abdominal pain	5	3.9%	1	1.0%
Anxiety	4	3.1%	1	1.0%
Sleep disturbance	4	3.1%	2	2.0%
Cataplexy	4	3.1%	1	1.0%
Diarrhea	4	3.1%	2	2.0%
Anorexia, decreased appetite	4	3.1%	0	0.0%
Vomiting	3	2.3%	0	0.0%

Reviewer Comment: Given the small number of patients in gender and age subgroups, no definitive conclusions about differential subgroup effects can be drawn. TEAEs in the Nervous System Disorders and Psychiatric Disorders SOCs were the most commonly reported in both males and females. Patients ≥ 65 years of age did not appear to experience a disproportionate amount of TEAEs. Patients with cataplexy had a similar adverse event profile as the general study population.

8.7. Specific Safety Studies/Clinical Trials

Not applicable to this application.

8.8. Additional Safety Explorations

8.8.1. Human Carcinogenicity or Tumor Development

Table 81 summarizes the neoplasms that were reported in the pitolisant clinical development program. Two patients who received pitolisant in the narcolepsy clinical trials reported neoplasms (see case narratives below); the other reported neoplasms occurred in Parkinson's disease and OSA trials.

- (b) (6): 68-year-old female with prior medical history of narcolepsy, pulmonary neoplasia, breast adenocarcinoma, cytomegalovirus hepatitis, diabetes, hypercholesterolemia, right bundle branch block, and recurrent urinary tract infections.

The patient was diagnosed with three lung nodules prior to inclusion in the study. 6 days after starting pitolisant, the patient underwent scheduled resection. She was subsequently hospitalized again to remove another nodule that was discovered during the first surgical procedure. The tumor was identified as a pulmonary carcinoid tumor.

- (b) (6): 46-year-old male with prior medical history of narcolepsy, compartment syndrome, obstructive sleep apnea, periodic leg movement syndrome, diabetes, hypertension, hypothyroidism, and pain syndrome. The patient had been diagnosed with malignant melanoma prior to enrollment in the study and underwent liver spot excision. An additional excision performed after study enrollment showed an absence of pathological findings.

Table 81: Neoplasms (Benign, Malignant, Unspecified) in Pitolisant Clinical Development Program - Pitolisant versus Placebo

STUDYID	USUBJID	TREATMENT GROUP	PREFERRED TERM
P0610	(b) (6)	Pitolisant	Pancreatic neoplasm
P0610		Pitolisant	Lung neoplasm malignant
P0611		Pitolisant	Melanocytic nevus
P0611		Pitolisant	Prostate cancer
P0908		Pitolisant	Sarcoma
P0908		Pitolisant	Skin papilloma
P0910		Pitolisant	Carcinoid tumor pulmonary
P1001		Pitolisant	Malignant melanoma
P0610		Placebo	Neuroendocrine tumor
P0610		Placebo	Basal cell carcinoma
P0610		Placebo	Renal cancer recurrent
P0610		Placebo	Renal cell carcinoma
P0611		Placebo	Prostate cancer

A patient receiving pitolisant in an ongoing study for OSA (HAROSA III, P15-13) reported an SAE of non-Hodgkin's lymphoma during the open-label phase. A patient in the US Expanded Access Program (HBS-101-CL-001) also reported an adverse event of lymphoma.

Reviewer comment: *The Applicant conducted two nonclinical carcinogenicity studies that did not find pathologic changes associated with pitolisant exposure. The neoplasms that were reported in the narcolepsy clinical trials predated the participants' exposure to pitolisant and appear to have no association with pitolisant treatment. Most neoplasms in the development program occurred in Parkinson's disease trials, which evaluated an older population that would have a higher baseline risk of developing neoplasms. Neoplasms were observed in both the pitolisant and placebo groups in Parkinson's disease trials. The nonclinical, clinical, and postmarketing data available thus far do not appear to suggest an association between pitolisant and development of neoplasms.*

8.8.2. Human Reproduction and Pregnancy

Four patients reported pregnancies in the narcolepsy clinical trials.

- (b) (6): 20-year-old female with narcolepsy who was treated with pitolisant in the open-label, long-term safety study (HARMONY III) became pregnancy 12 months after the initiation of treatment. The patient elected to terminate the pregnancy and continued pitolisant treatment. She became pregnant again 15 months later and carried the pregnancy to term. No maternal complications, prematurity, malformations, or neonatal complications were reported.

- (b) (6) 34-year-old female with narcolepsy who was treated with pitolisant in the open-label, long-term safety study (HARMONY III) reported a miscarriage (approximately 7 weeks gestation) after 5 months of pitolisant treatment. The patient had been on an oral contraceptive during the study. Pitolisant treatment was discontinued.

- (b) (6) 29-year-old female with narcolepsy who was treated with pitolisant in the open-label, long-term safety study (HARMONY III) became pregnant 2 years after starting pitolisant. Pitolisant was discontinued and the patient continued the pregnancy. The infant was born prematurely (birthweight 1.9 kg) but no fetal distress, malformations, neonatal complications, or maternal complications were reported.

- (b) (6): 34-year-old female with narcolepsy who received placebo in HARMONY I had a positive urine pregnancy test at Visit 6 and was withdrawn from the study.

As of the 120-day safety update, nine patients spontaneously reported pregnancies in the post-marketing period; two of these pregnancies ended in miscarriage (Table 82).

Table 82: Spontaneous Reports of Pregnancy in Patients Receiving Pitolisant in the Post-Marketing Period 31 March 2016 Through 31 March 2018

Case Number	Country	Age (years)	Pitolisant Treatment Dates		Delivery Process	Infant Malformation	Infant Clinical Event
			Start	Stop			
(b) (6)	FR	34	2013	16 Oct 2016	Normal	No	No
	FR	22	03 Oct 2013	20 Dec 2015	Cesarean	No	Yes[a]
	FR	40	25 Apr 2015	Ongoing	Miscarriage	NA	NA
	FR	32	17 Sep 2013	Ongoing	Voluntary abortion	NA	NA
	DE	26	01 May 2015	11 Sep 2015	Miscarriage	NA	NA
	FR	UKN	UKN	UKN	Normal	No	No
	IT	31	07 Oct 2017	UKN	Normal	No	No
	FR	22	31 Jul 2017	07 Jun 2018	Voluntary abortion	NA	NA
	FR	32	Sep 2018	Sep 2018	Pregnancy Ongoing	No	NA

DE=Germany; FR=France; IT=Italy; NA=not applicable; UKN=unknown
[a] Neonatal urinary tract infection was reported as Case (b) (6) (Table 88)
Source: Periodic Benefit Risk Evaluation Report No 4, dated 01 June 2018 (PSUSA/00010490/201803), Section 6.3 and 4 Month (Day 120) Safety Update, pages 26-27.

The Division of Pediatric and Maternal Health (DPMH) was consulted for additional review of this application (review completed by Dr. Carrie Ceresa PharmD, MPH) and provided language for labeling consistent with the Pregnancy and Lactation Labeling Rule (PLLR). DPMH determined that a pregnancy registry, an additional pregnancy study, and a lactation study should be conducted (see Section 12, Postmarketing Requirement and Commitments).

Reviewer Comment: Limited information about the use of pitolisant is pregnancy is available, as pregnant women were excluded from clinical trials and clinical trial protocols required the use of contraception in patients with child-bearing potential. To date, no fetal or neonatal abnormalities have been reported following pitolisant exposure in pregnancy. Miscarriage was reported in the open-label clinical trial and in the post-marketing period; however, given the small number of cases, the lack of placebo-controlled data, and the relatively high baseline rates of miscarriage in the population, no conclusions about an association between pitolisant and miscarriage can be made from this data.

8.8.3. Pediatrics and Assessment of Effects on Growth

The Applicant is conducting a randomized, double-blind, placebo-controlled study to evaluate the effect of pitolisant on EDS and cataplexy in patients aged 6 to 18 years (Study P11-06). No SAEs had been reported by the 120-day safety update submission date. The study is ongoing, and no additional data are available. The Applicant has also conducted Study P11-11, a single dose trial to evaluate the pharmacokinetics of pitolisant in children aged 6 to 18 years. This study enrolled 24 children with narcolepsy and tested a single dose of 20 mg once daily. TEAEs reported in the study included headache and dizziness. No SAEs were reported. Per the study report, no clinically significant abnormalities in vital signs, laboratory assessments, physical examinations, or ECGs were observed. The Applicant found higher exposures in pediatric patients as compared with young adult patients, independent of body weight or gender.

This application was exempt from PREA because of pitolisant's orphan drug designation.

8.8.4. Overdose, Drug Abuse Potential, Withdrawal, and Rebound

Data from nonclinical studies, human liability studies and clinical trials indicate that pitolisant does not carry a significant abuse potential. Please refer to Section 8.5.4 for description of data related to overdose, drug abuse potential, withdrawal and rebound.

8.9. Safety in the Postmarket Setting

8.9.1. Safety Concerns Identified Through Postmarket Experience

Pitolisant has been authorized in the European Union since March 2016. Although fully authorized throughout the European Union (EU), pitolisant is currently marketed in Belgium, France, Germany, Ireland, Italy, and the United Kingdom. Patients in Spain, the Netherlands, and Switzerland have access to pitolisant via a Compassionate Use Program (CUP). The Division of Pharmacovigilance (DPV) within the Office of Surveillance and Epidemiology (OSE) provided a consultative review of the available postmarketing safety data (by reviewers Dr. Kelly Harbourt, PharmD and Robert Levin MD). DPV reviewed the Applicant's Periodic Benefit Risk Evaluation Report, Number 4 (PBRER-4) and postmarketing reports of adverse events submitted to the Vigibase, FDA Adverse Event Reporting System (FAERS), and EudraVigilance databases. I reviewed the PBRER-4 and the EudraVigilance database as well.

DPV did not propose any additional regulatory actions for further safety review. DPV noted that two cases of suicidal ideation and one case of mania were identified in the previous reporting period and that the Applicant plans to perform cumulative reviews for these events. DPV also submitted an information request to EMA through the FDA-EMA Pharmacovigilance Cluster. EMA reported that they had not identified signals for abuse, misuse, withdrawal, dependence, seizure, QT interval prolongation or arrhythmia, suicidal behavior, depression, anxiety, or irritability. For additional details from the DPV consult, including full case narratives, please refer to the archived review in DARRTS. The Executive Summary and a summary of the DPV search strategy are included in Appendix 13.6.

PBRER-4: The Applicant submitted PBRER-4 for the reporting interval spanning October 1, 2017 to March 31, 2018 with the NDA. The Applicant also provided a summary of safety concerns, which outlines known and potential risks and information that is still needed to fully characterize the safety profile (Table 83). At the time of PBRER-4, the cumulative exposure to pitolisant, in patient-years, was 2597 (based on a daily dose of 18 mg).

Table 83: Applicant's Summary of Safety Concerns

Important identified risks	Insomnia Gastric disorders w/hyperacidity Anxiety Depression Weight increase Adverse effects as a result of increased exposure in patients • with impaired hepatic function, or renal impairment • co-administration with CYP2D6 inhibitors, • CYP2D6 genetic polymorphism
Important potential risks	Proconvulsive potential QT interval prolongation. Fertility disorders Exposure during pregnancy and lactation Interaction w/ drugs w/ histamine H1 receptor antagonism activity. Drug abuse and misuse Drug dependence Rebound effect
Missing information	Long-term safety data Pharmacokinetic interactions Pediatric patients (efficacy and safety data) Patients with severe hepatic impairment (Child Pugh C) Patients with severe renal impairment (creatinine clearance <15 ml/min) Patients with underlying severe cardiovascular diseases Patients with severe depression and severe anxiety

Source - PBRER-4, Table 11, page 26

During the most recent PBRER reporting period, 6 patients reported 15 SAEs:

- Arrythmia (male patient of unknown age with prior history of arrhythmia on modafinil, indication for pitolisant use unknown)

- hot flashes, headache, sleep disturbance, suicidal ideation, worsened depression, and agitation, confusional state, gastrointestinal disorder (35-year-old female with prior history of hypersomnia, anxiety, and depression)

- irritability, insomnia, and abnormal behavior (53-year-old male with prior history of depression, indication for pitolisant use unknown)

- seizure requiring hospitalization (22-year-old female with prior history of narcolepsy and well-controlled generalized idiopathic epilepsy)

- severe depression with suicidal risk (18-year old female prior history of hypersomnia and depression)

- depression (26-year-old female with hypersomnia)

Vigibase: Vigibase is the World Health Organization global database of individual case safety reports (ICSRs). Vigibase has received 121 reports related to pitolisant in the postmarketing period. As per the DPV review, the MedDRA Preferred Terms (PTs) with ≥ 4 reports in the Vigibase and FAERS databases include: insomnia (16 cases), headache (15), nausea (8), depression (7), irritability (6), pruritis (6), anxiety (5), abnormal dreams (4), depressed mood (4), fatigue (4), hallucination (4), nightmare (4), sleep disorder (4), and weight increased (4).

FAERS: The FAERS database contains adverse event and medication error reports that have been submitted to the FDA. Four SAEs have been reported to the FAERS database in the postmarketing period:

- idiopathic stroke (35-year-old female with past medical history of hypersomnia and atrial septal defect and who was concomitantly prescribed pitolisant, pregabalin, methylphenidate, mometasone, paracetamol, polyethylene glycol, and an oral contraceptive)

- manic episode (53-year-old male with narcolepsy, sleep apnea, migraine, hyperlipidemia, diverticulosis, renal calculus, but no prior psychiatric history who was concomitantly prescribed pitolisant, modafinil, and paroxetine prior to episode)

- splenic infarction (48-year-old female with history of narcolepsy, deep vein thrombosis, tobacco use who was also prescribed venlafaxine and methylphenidate)

- pollakiuria, “malaise during sexual act when lying down,” “head spinning and feeling of absence” (male patient of unknown age with history of hypersomnia and asthma)

EudraVigilance: The European Medicines Agency’s EudraVigilance website is a publicly available system for reporting suspected adverse drug reactions. The database can be accessed at http://www.adrreports.eu/en/index.html.

I searched the EudraVigilance database for safety signals originating from postmarketing reports. A total of 65 individual cases were reported to EudraVigilance for pitolisant by

February 2019. I searched for pitolisant in the database of suspected adverse drug reaction reports for substances and obtained a line listing of suspected adverse drug reactions for the years 2016 to 2019. The search included adverse drug reactions of all levels of seriousness, geographic origins, reporter groups, genders, and ages. I reviewed the individual case safety report forms (ICSR) for potentially life-threatening adverse events and adverse events of special interest including psychiatric adverse events, hepatic effects, cardiovascular effects, and seizures/convulsions.

Most suspected adverse drug reactions occurred in female patients (67.7%).
Non-Sleep-Related Psychiatric Adverse Events

- Anxiety was reported in a 54-year-old male who was also prescribed modafinil. The patient recovered. The ICSR did not contain any additional clinical information.

- Fear of death, insomnia, and somnolence were reported in a 50-year-old male prescribed pitolisant 36 mg for narcolepsy. The dose was not changed. The patient did not recover. The ICSR did not contain any additional clinical information.

- Depressed mood, feeling of despair, and malaise were reported in a 16-year-old female who had taken pitolisant 9 mg for 3 days for narcolepsy. The patient was also receiving sodium oxybate (unknown dose), fluoxetine 20 mg, and ethinylestradiol/levonorgestrel (unknown dose). The patient did not recover. The ICSR did not contain any additional clinical information.

- Abnormal behavior, euphoric mood, hypomania, insomnia, irritability, and mania occurred in a 53-year-old male taking pitolisant 36 mg for narcolepsy. The patient was also prescribed paroxetine 20 mg for depression, fenofibrate for hypercholesterolemia, and modafinil for narcolepsy. Pitolisant and paroxetine were withdrawn. The action taken with modafinil is unknown. Fenofibrate was continued at the same dose. The symptoms resulted in a prolonged hospitalization. Mania was reported to have resolved but euphoric mood had not resolved. The status of other suspected drug reactions in this case is unknown.

- Anxiety, gastrointestinal disorder, and decreased GFR occurred in a 72-year-old woman who was prescribed pitolisant for narcolepsy. The dose of pitolisant was reduced. Anxiety and gastrointestinal disorder resolved, but decreased GFR did not resolve.

- Crying, decreased appetite, depressed mood, migraine, muscle spasms, and vomiting were reported in a 31-year-old female taking pitolisant 9 mg for narcolepsy. The patient was also prescribed irbesartan (unknown dose) and etonogestrel (unknown dose). The dose of pitolisant was increased. The symptoms resolved.

- Abulia, anhedonia, depressed mood, and social avoidant behavior occurred in a 28-year-old male taking pitolisant 18 mg for hypersomnia. The drug was withdrawn. The symptoms were not resolved at the time of the report. The ICSR did not contain any additional clinical information.

- Agitation, confusional state, depression, gastrointestinal disorder, headache, hot flush, sleep disorder, and suicidal ideation in a 35-year-old-female prescribed pitolisant for hypersomnia. The patient was also prescribed esomeprazole and venlafaxine. The status of the symptoms is unknown. The ICSR did not contain any additional clinical information.

- A suicide attempt was reported in a female of unknown age prescribed pitolisant for idiopathic hypersomnia. The outcome is unknown. The ICSR did not contain any additional clinical information.

- Abnormal dreams, anxiety, and insomnia occurred in a 19-year-old female prescribed 9 mg of pitolisant. Action taken with pitolisant was unknown. The patient recovered. The ICSR did not contain any additional clinical information.

- Depression was reported in an 18-year-old female prescribed pitolisant for idiopathic hypersomnia. Pitolisant was withdrawn. The ICSR did not contain any additional clinical information.

- Abnormal behavior and psychomotor hyperactivity were reported in an 18-year-old female prescribed pitolisant 18 mg for narcolepsy. The patient was hospitalized. Pitolisant was withdrawn. The patient's status is unknown. The ICSR did not contain any additional clinical information.

- Abnormal dreams, aggression, disturbance in attention, insomnia, night sweats, and tinnitus were reported in a 49-year-old female who was prescribed pitolisant 18 mg for hypersomnia. The pitolisant dose was reduced. The patient had not recovered at the time of the report. The ICSR did not contain any additional clinical information.

- Depression was reported in a 26-year-old female who was prescribed 20 mg of pitolisant hydrochloride for idiopathic hypersomnia. The patient was also prescribed dexamfetamine sulfate, etonogestrel, and gabapentin. Pitolisant was withdrawn. The patient had not recovered at the time of the report. The ICSR did not contain any additional clinical information.

Cardiovascular Adverse Events

- Chest discomfort, palpitations, and increased weight were reported in a 40-year-old female prescribed pitolisant 18 mg for narcolepsy. The patient was also prescribed

levetiracetam and lamotrigine (unknown doses) for epilepsy. Pitolisant was withdrawn. The patient recovered.

- Palpitations were reported in a 38-year-old female prescribed pitolisant 36 mg or 113 days for narcolepsy. The patient was also prescribed baclofen, betamethasone, tramadol, fluticasone/salmeterol, salbutamol, ethinylestradiol/levonorgestrel, and omeprazole (unknown doses and indications). Pitolisant was withdrawn. The patient had not recovered at the time of the report.

- Arrhythmia occurred in a male (unknown age) who was prescribed pitolisant 18 mg for narcolepsy. The patient was hospitalized. Action taken with pitolisant is unknown. The patient had not recovered at the time of the report. The ICSR did not contain any additional clinical information.

Seizures/Convulsions

- A case of myoclonic epilepsy occurred in a 26-year-old female who took pitolisant (dose unspecified) for 10 days for idiopathic hypersomnia. The drug was withdrawn. The patient was also prescribed valproic acid. The patient recovered. The ICSR did not contain any additional clinical information.

- Epilepsy was reported in a 24-year-old female who was prescribed pitolisant 9 mg for narcolepsy. The patient was hospitalized. Pitolisant was withdrawn. The patient recovered. The ICSR did not contain any additional clinical information.

Potentially Life-Threatening Adverse Events

- Splenic infarction occurred in a 48-year-old female who was prescribed pitolisant 18 mg for narcolepsy. The patient was also prescribed venlafaxine (unknown dose) and methylphenidate (unknown dose). The patient was hospitalized. Methylphenidate was withdrawn. The doses of pitolisant and venlafaxine were not changed. The patient recovered. The ICSR did not contain any additional clinical information.

- Appendicitis was reported in a 48-year-old male who was prescribed pitolisant 18 mg (for 476 days) and 26 mg (for 497 days) for narcolepsy. The patient was hospitalized. Pitolisant was withdrawn. The patient recovered. The ICSR did not contain any additional clinical information.

- Deep vein thrombosis and pulmonary embolism were reported in a 34-year-old male taking pitolisant 4.5 mg for narcolepsy. The patient was hospitalized. Pitolisant was withdrawn. The patient was reported to be recovering. The ICSR did not contain any additional clinical information.

- An endocrine neoplasm was reported in a 15-year-old female who was prescribed pitolisant 18 mg for narcolepsy. The patient was hospitalized. Action taken with pitolisant is unknown. The patient's status is unknown. The ICSR did not contain any additional clinical information.

Reviewer comment: Neither my analysis of the postmarketing data nor DPV's review identified any new or unexpected safety signals. DPV notes that the total patient exposure to pitolisant is still low.

Psychiatric adverse events have been reported in the postmarketing period, including 1 suicide attempt and 1 report of a manic episode. However, psychiatric conditions are prevalent in patients with narcolepsy and these spontaneous reports, without comparative data in a control population, do not establish a clear association with pitolisant. The postmarketing safety data regarding psychiatric adverse events appear to be consistent with the safety data from clinical trials.

The information provided regarding the spontaneous reports of epilepsy in patients taking pitolisant are insufficient to determine whether epilepsy was related to drug effects in these cases. Reports of seizures should continue to be monitored in the postmarketing period given the nonclinical findings of convulsions in rodents.

The surveillance databases contain few reports about cardiovascular events and no cases of prolonged QT interval. No pattern connected the potentially life-threatening adverse events that were reported. No reports of drug-induced liver injury were reported.

8.9.2. Expectations on Safety in the Postmarket Setting

The most frequent reason for off-label use in the postmarketing period was idiopathic hypersomnia. In the reviews conducted by both the Applicant and DPV, the safety signals in patients with hypersomnia did not differ significantly from those in the narcolepsy population. Safety data obtained thus far from postmarketing pharmacovigilance has revealed a safety profile that is consistent with clinical trial data.

8.9.3. Additional Safety Issues from Other Disciplines

Convulsions were observed in nonclinical studies in rodents. As per Dr. Miller's nonclinical review, "the proconvulsant potential of pitolisant was assessed by pentylenetetrazol (PTZ) challenge in Swiss mice. Oral administration of pitolisant increased central excitation as demonstrated by increased incidence of tremors and spasms at 30 mg/kg as well as straub tail and convulsions at 60 mg/kg after challenge with sub-convulsant exposure to PTX (30 mg/kg, i.p.). Although both tremors and spasms occurred in control animals after PTC challenge, the latency time was significantly reduced at the 2 highest doses of pitolisant. Pitolisant was

determined to be proconvulsant at 30 and 60 mg/kg." Studies in rats also demonstrated that both pitolisant and its major circulating metabolite in rats (BP1.2526) induced convulsions when administered intravenously.

8.10. Integrated Assessment of Safety

In the narcolepsy development program, the most common TEAEs were headache, insomnia, nausea, upper respiratory infection, musculoskeletal pain, anxiety, increased heart rate, hallucinations, irritability, dizziness, abdominal pain, and anorexia. SAEs were rare in the narcolepsy development program and no consistent pattern linking the SAEs could be discerned.

No unexpected safety signals emerged from analysis of laboratory, vital signs, or ECG datasets.

QT studies demonstrated pitolisant's QT prolonging potential at exposures greater than expected at recommended doses. However, clinically significant QT prolongation was not observed in the narcolepsy clinical trials. More pitolisant-treated patients reported cardiac and vascular disorders than patients in the placebo group, though the absolute number of cardiovascular adverse events was small and postmarketing data have not indicated a strong signal for cardiovascular events.

Psychiatric conditions such as depression and anxiety are more common in the narcolepsy population. Nonetheless, patients receiving pitolisant appeared to experience non-sleep-related psychiatric adverse events more frequently than patients treated with placebo. The available data from clinical trials and from the postmarketing period do not suggest that pitolisant-treated patients are at increased risk of suicidal ideation or suicidal behaviors. However, these data are limited both by the relatively small number of patients in clinical trials and the use of the BDI-SF (which does not capture the full spectrum of suicidal thoughts and behaviors) as the suicide assessment tool in clinical trials.

Although convulsions were observed at high doses in nonclinical trials, the totality of the clinical trial data and the available postmarketing reports do not indicate a higher risk of seizures in patients taking pitolisant at recommended doses.

Overall, the risks associated with pitolisant use at recommended doses in the narcolepsy appear to be manageable in the context of standard clinical care. The demonstrated benefits of pitolisant on EDS in patients with narcolepsy outweigh the risks of use in this population.

9. Advisory Committee Meeting and Other External Consultations

Although pitolisant is a new molecular entity, it has been authorized and in use in the European Union for 3 years. The safety review of pitolisant was consistent with the known safety profile from available European postmarketing data. The clinical trial designs and statistical methods

were conventional. The review did not prompt any questions that would have required input from an Advisory Committee. The Division did seek external consultation with EMA to discuss its initial safety and efficacy review and ongoing postmarketing surveillance. The Division communicated via teleconference with EMA on March 11, 2019 to discuss issues related to the application, including the adverse event profile, long-term safety of the 40 mg dose, and human abuse liability. EMA noted that the available long-term safety data for the 40 mg dose are limited but that, on balance, the overall safety profile and the potential benefit demonstrated in the clinical studies supported authorization. EMA pointed to the ongoing post-authorization safety study as a mechanism for obtaining additional long-term data. (b) (4)

10. Labeling Recommendations

10.1. Prescription Drug Labeling

The proposed label has been drafted in accordance with the Physician Labeling Rule and the Pregnancy and Lactation Labeling Rule.

Indications and Usage: The Applicant has proposed two indications–treatment of EDS in adult patients with narcolepsy and treatment of cataplexy in adult patients with narcolepsy. The Division has concluded that, although the HARMONY CTP study provides some evidence of effectiveness in patients with cataplexy, confirmatory data would be required prior to granting an indication for cataplexy. The Division has determined that pitolisant is indicated to treat excessive daytime sleepiness in adult patients with narcolepsy.

Dosage and Administration: 5 mg, 20 mg, and 40 mg pitolisant hydrochloride are equivalent to 4.45 mg, 17.8 mg, and 35.6 mg pitolisant free base, respectively. Pitolisant dosage in labeling is presented in free base form. A salt-free base equivalency statement should be included in labeling.

The following dose titration schedule is outlined in labeling:

The recommended dosage range is 17.8 mg to 35.6 mg daily. Titrate dosage as follows:

Week 1: initiate with a dose of 8.9 mg (two 4.45 mg tablets) once daily

Week 2: increase dose to 17.8 mg (one 17.8 mg tablet) once daily

Week 3: may increase to the maximum recommended dose of 35.6 mg (two 17.8 mg tablets) once daily

In patients with moderate hepatic impairment, moderate renal impairment, and severe renal impairment, the maximum dosage should be 17.8 mg once daily. Pitolisant is not recommended in patients with end stage renal disease. The maximum dose should be 17.8 mg in patients who are concomitantly taking strong CYP2D6 inhibitors or who are known to be poor metabolizers of CYP2D6; pitolisant dose should be halved in patients on stable doses of pitolisant who start receiving strong CYP2D6 inhibitors.

(b) (4)

Contraindications: (b) (4) The Division has (b) (4) recommended a contraindication in patients with severe hepatic impairment. Although effects in patients with severe hepatic impairment were not directly studied in clinical trials, the data from patients with mild and moderate hepatic impairment suggest that increased exposures–and, therefore, increased risk for QT prolongation–would be anticipated in patients with severe hepatic impairment. Use in patients with severe hepatic impairment is also listed as a contraindication in the EMA label.

Warnings and Precautions: The labeling contains a warning about pitolisant's potential to prolong the QT interval.

Adverse Reactions: Adverse reactions from HARMONY I, HARMONY CTP, and HARMONY I-bis were pooled in labeling. As noted above, the unweighted rates of adverse events did not differ significantly from the weighted rates (which accounted for differences in randomization ratios in the clinical trials). For simplicity, unweighted values were included in the label. Headache was the most frequent adverse reaction overall. The adverse reactions that occurred in ≥ 5% of patients and at rates twice that of the placebo population were insomnia, nausea, and anxiety. The label also includes adverse events that occurred in ≥ 2% of patients and more frequently in the placebo group: headache, insomnia, nausea, upper respiratory infection, heart rate increased, hallucinations, irritability, abdominal pain, sleep disturbance, decreased appetite, cataplexy, dry month, and rash. Adverse reactions that have been reported to surveillance databases are also listed in labeling. Adverse reactions with ≥ 4 postmarketing reports and adverse reactions of special interest (e.g., epilepsy, suicidal ideation) are including in this listing.

Drug Interactions: Clinically important interactions with pitolisant can be expected with concomitant use of strong CYP2D6 inhibitors and inducers, Histamine 1 (H1) antagonists, drugs that prolong the QT interval, and sensitive CYP3A4 substrates.

Use in Special Populations: DPMH has recommended a prospective and observational pregnancy registry as well as an additional complimentary pregnancy study that uses a different

design from the registry such as a case control or a retrospective study using a claims or electronic medical records with outcome validation.

Pitolisant is likely to be present in human milk. Clinical trials and postmarketing reports to date do not provide information about pitolisant's effects on breastfeeding. DPMH has recommended a postmarketing lactation study.

Pitolisant may reduce the effectiveness of oral contraceptives.

Although pitolisant is not indicated for use in pediatric population, the Division has included available pediatric PK data in labeling. Pitolisant exposures are 2-fold higher in pediatric patients aged 12 to < 18 years and 3-fold higher in patients aged 7 to 12 years.

Clinical Studies: (b) (4) The Division has included only results of analyses of pre-specified primary endpoints.

10.2. Nonprescription Drug Labeling

This section is not applicable for this application.

11. Risk Evaluation and Mitigation Strategies (REMS)

The safety review of this product did not reveal any serious risks that require risk management strategies beyond describing the risks and benefits of the product in labeling. Therefore, a REMS is not recommended.

12. Postmarketing Requirements and Commitments

DPMH has determined that postmarketing studies to obtain data on pregnancy and lactation should be required. Please see the DPMH review for full details of the consultative review. DPMH has outlined the following postmarketing requirements:

1) The applicant should be required to conduct a prospective, registry based observational exposure cohort study that compares the maternal, fetal, and infant outcomes of women exposed to pitolisant during pregnancy to an unexposed control population. The registry will detect and record major and minor congenital malformations, spontaneous abortions, stillbirths, elective terminations, small for gestational age, preterm birth, and any other adverse pregnancy outcomes. These outcomes will be assessed throughout pregnancy. Infant outcomes, including effects on postnatal growth and development, will be assessed through at least the first year of life.

2) The applicant should be required to conduct an additional pregnancy study that uses a different design from the Pregnancy Registry (for example a case control study or a retrospective cohort study using claims or electronic medical record data with outcome validation) to assess major congenital malformations, spontaneous abortions, stillbirths, and small for gestational age and preterm birth in women exposed to pitolisant during pregnancy compared to an unexposed control population.

3) The applicant should be required to conduct a lactation study in lactating women who have received therapeutic doses of pitolisant using a validated assay to assess concentrations of pitolisant in breast milk.

13. Appendices

13.1. References

1. Beck, AT and RW Beck, 1972, Screening Depressed Patients in Family Practice, Postgrad Med, 52(6):81–85.

2. Division of Sleep Medicine, Harvard Medical School, 2018, http://healthysleep.med.harvard.edu/narcolepsy/what-is-narcolepsy/science-of-narcolepsy, accessed 1/29/2019, 3/22/2019.

3. Johns, M, 2019, The Official Website of the Epworth Sleepiness Scale, https://epworthsleepinessscale.com/about-the-ess, accessed July 2019.

4. Kornum, BR, S Knudsen, HM Ollila, F Pizza, PJ Jennum, Y Dauvilliers, and S Overeem, 2017, Narcolepsy, Nat Rev, 3:1–19.

5. Sateia, MJ, 2014, International Classification of Sleep Disorders–Third Edition: Highlights and Modifications, Chest, 146(5):1387–1394.

6. Scammell, TE, 2015, Narcolepsy, N Engl J Med, 373:2654–2662.

7. Thorpy MJ and AC Krieger, Delayed Diagnosis of Narcolepsy: Characterization and Impact, 2014, Sleep Med, 15:502–507.

13.2. Financial Disclosure

Covered Clinical Study (Name and/or Number): All Covered Clinical Studies Submitted in Support of the Application

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 75		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 0		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: N/A Significant payments of other sorts: N/A Proprietary interest in the product tested held by investigator: N/A Significant equity interest held by investigator in S Sponsor of covered study: N/A		
Is an attachment provided with details of the disclosable financial interests/arrangements: N/A	Yes ☐	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided: N/A	Yes ☐	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 0		
Is an attachment provided with the reason: N/A	Yes ☐	No ☐ (Request explanation from Applicant)

13.3. Table of Clinical Trials

Table 84: Table of Clinical Trials, Pitolisant Development Program, All Indications

Type of Study	**Study Identifier**	**Location of Study Report**	**Main Objective of the Study**	**Study Design and Type of Control**	**Test Product(s); Dosage Regimen; Route of Administration**	**Number of Subjects (#M/F)**	**Healthy Subjects or Diagnosis of Patients**	**Duration of Treatment**	**Study Status; Type of Report**
BA/PK	P03-01	5.3.1.2	Comparative BA of tablet versus capsule taken with and without grapefruit juice	Open, randomized, 2-way cross-over	Tablets 20 mg and Capsules 20 mg 20 mg / dose x 3 periods Oral route	8 (M)	Healthy volunteers	3 single doses 5 weeks	Completed Full Report
PK/PD	P04-06	5.3.3.1	PK of repeated doses up to 28 days	Open-label	Tablets 20 mg and 10 mg Doses: 40 mg/ day for 14d and 50 mg/day for 14d Oral route	6 (M)	Healthy volunteers	Repeated doses 28 days	Completed Full Report
PK	P09-14	5.3.3.1	To investigate the effect of hepatic impairment on the PK of pitolisant and its main metabolite following a single oral dose of 20 mg	Open-label, Parallel group	Tablets 20 mg Dose: 20 mg Oral route	24 (18M/6F)	12 healthy volunteers (normal hepatic function)/ 12 patients with impaired hepatic function	1 single dose	Completed Full Report

PK/PD	P11-01	5.3.3.1	Mass balance study, metabolic profile	Open-label	[^{14}C] 20 mg capsules Dose: 20 mg Oral route	6 (M)	Healthy volunteers	1 single dose 5 weeks	Completed Full Report

Type of Study	Study Identifier	Location of Study Report	Main Objective of the Study	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Number of Subjects (#M/F)	Healthy Subjects or Diagnosis of Patients	Duration of Treatment	Study Status; Type of Report
PK	P15-02	5.3.3.1	Mass balance study at steady state in CYP2D6 genotyped subjects	Open Label, Single-Period Repeated Dose Study	20 mg tablets Dose: 20 mg/day from Day 1 to Day 7 with [^{14}C] pitolisant dose on Day 8 Oral route	8 (M)	Healthy volunteers	Repeated doses 8 days	Completed Full Report
PK/tolerability	P11-11	5.3.3.2	PK in patients from 6 to <18 years old	Open-label	20 mg tablets Dose: 20 mg Oral route	25 (12M/13F)	Patients with narcolepsy aged 6 to <18 yrs	1 single dose 6 days	Completed Full Report
QT	P09-11	5.3.3.3	Effect of 2 doses (40 and 120 mg) on QTcF	Randomized, double-blind, 4- period, cross over,	Tablets 20 mg Doses: 40 mg and 120 mg Oral	58 (25M/33F)	Healthy volunteers	1 single dose	Completed Full Report
PK	P09-12	5.3.3.3	The evaluation of the safety and PK of oral repeated 20 mg doses of pitolisant	Open-label, Parallel group	Tablets 20 mg One dose per day: 20 mg Oral route	25 (12M/13F)	Healthy (elderly) volunteers (≥68 yrs) and young adult control	Repeated doses 14 days	Completed Full Report

PK	P09-13	5.3.3.3	To investigate the effect of renal impairment on the PK of pitolisant and its main metabolite following a single oral dose of 20 mg	Open-label, Parallel group	Tablets 20 mg Dose: 20 mg Oral route	25 (21M/4F)	13 healthy volunteers (normal renal function)/12 patients with renal impairment	1 single dose	Completed Full Report

Type of Study	Study Identifier	Location of Study Report	Main Objective of the Study	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Number of Subjects (#M/F)	Healthy Subjects or Diagnosis of Patients	Duration of Treatment	Study Status; Type of Report
QT	P14-05	5.3.3.3	Effect of 3 doses (160, 200 and 240 mg) on QTcF interval	Randomized, double blind, single dose, placebo-controlled	Tablets 20 mg Doses: 160 mg, 200 mg and 240 mg Oral route	25 (25M)	Healthy male volunteers	1 single dose	Completed Full Report
[redacted]								(b) (4)	Ongoing Not Applicable
PK/PD	P03-08	5.3.3.4	The evaluation of the interaction of pitolisant 60 mg on olanzapine 5	Open-label	20 mg tablets Pitolisant Dose: 60 mg Olanzapine dose: 5 mg Oral route	6 (M)	Healthy volunteers	1 single dose 24 days (+ follow-up)	Completed Full Report
PK	P11-03 Part I Part II Part III	5.3.3.4	To assess the impact of concomitant food intake on the relative bioavailability of pitolisant	Open, 2-way cross- over	Tablets 20 mg 20 mg / dose x 2 Oral route	13/19/19 (M)	Healthy volunteers	1 single dose on two occasions (fed/fasted) with a 7-day	Completed Full Report Full Report Full Report

PK	P11-10	5.3.3.4	To assess whether single dose pitolisant (20 mg) oral bioavailability and main PK parameters were modified by concomitant administration of rifampicin	Cross-over, single sequence, two- period, open label	20 mg tablets 1 dose: 20 mg Oral route	19 (M)	Healthy volunteers	1 single dose on two occasions (Day 1 and at Day 14)	Completed Full Report

Type of Study	Study Identifier	Location of Study Report	Main Objective of the Study	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Number of Subjects (#M/F)	Healthy Subjects or Diagnosis of Patients	Duration of Treatment	Study Status; Type of Report
PK	P14-07 Part I Part II	5.3.3.4	Pharmacokinetic interaction with sodium oxybate and modafinil	Cross-over, open label, two-part, 2-way, reciprocal drug-drug (sodium oxybate), one sequence (modafinil)	20 mg tablets 1 dose: 20 mg Oral route	16 (M)	Healthy volunteers	1 single dose	Completed Full Report Full Report
PK	P15-15 Part I Part II	5.3.3.4	Pharmacokinetic interaction (at steady- state) with midazolam and bupropion Pharmacokinetic interaction (at steady- state) with probenecid	Two-part, open label, one sequence, cross-over Two-part,	20 mg tablets Dose: 40 mg/day from Day 7 to Day 18 Oral route 20 mg tablets Dose: 40 mg/day at Day 1 and Day 11 Oral route	18 (M) 18 (M)	Healthy volunteers Healthy volunteers	Repeated doses 12 days 1 single dose	Completed Full Report Completed Full Report

Pop-PK	PH14056	5.3.3.5	To develop a population PK model for pitolisant in adults and to evaluate dose proportionality after single and multiple dose administration, plus PK linearity across time	Data were pooled from 6 studies (3 single oral dose and 3 multiple oral dose regimens)	single dose varying from 20 mg to 120 mg; and repeated doses ranging from 20 to 60 mg/day	120 (74M/46F)	Healthy volunteers (male and female)	Single dose or Repeated doses for 9, 14, or 28 days	Completed Full Report

Type of Study	Study Identifier	Location of Study Report	Main Objective of the Study	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Number of Subjects (#M/F)	Healthy Subjects or Diagnosis of Patients	Duration of Treatment	Study Status; Type of Report
Dose-Modeling	HBS-101-NPS2940-RPT001	5.3.3.5	Establish a model to describe the daily cataplexy counts (sum of partial and complete events) over time. Evaluate the dose-response relationship of pitolisant on the time course of the daily cataplexy counts over time. Evaluate the effects of covariates on the baseline and dose-	Data were pooled from 5 repeat dose studies	Tablets: 20 mg; Repeated doses ranging from 5 to 40 mg/day Oral route	219 (124M/95F)	Patients with narcolepsy	Repeated doses: P07-03, P09-15, and P10-01: 8 weeks P11-05: 7 weeks P09-10: 1 year; 5 year Extension (French Cohort)	Completed Full Report

PK/PD	P02-02	5.3.4.1	Safety, PK/PD after 6 single ascending doses	Rando mized Parallel, Double-blind placebo-controlled, six parallel group	Tablets 1 mg, 10 mg, 20 mg 1 mg, 5 mg, 10 mg, 20 mg, 40 mg, or 60 mg dose Oral route	36 Pitolisant (N=30) Placebo (N=6) (M)	Young healthy volunteers	1 single dose	Completed Full Report

Type of Study	Study Identifier	Location of Study Report	Main Objective of the Study	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Number of Subjects (#M/F)	Healthy Subjects or Diagnosis of Patients	Duration of Treatment	Study Status; Type of Report
PK/PD	P03-03	5.3.4.1	Safety, PK, and PD (feeding behavior and satiety), of 2 multiple doses in young healthy volunteers	Randomized parallel, double-blind, placebo-controlled	Tablets 20 mg 40 mg / day Oral route	8 Pitolisant (N=6), Placebo (N=2) (M)	Young healthy volunteers	Repeated doses 9 days	Completed Full Report
PK/PD	P03-04	5.3.4.1	Safety, PK/PD after single oral doses of 90 and 120 mg	Randomized parallel, double-blind, placebo-controlled.	Tablets 20 mg 90 mg and 120 mg /dose Oral route	12 90 mg pitolisant (N=5) 120 mg pitolisant (N=5) placebo (N=2) (M)	Healthy volunteers	1 single dose	Completed Full Report
PD	P16-02	5.3.4.1	To assess the abuse potential of single doses of pitolisant relative to phentermine HCl and placebo	Randomized, double-blind, placebo-controlled, Active-controlled, crossover	Tablets 20 mg Doses: 40 or 240 mg Oral route	43 (31M/12F)	Healthy, non-dependent recreational stimulants users	1 single dose	Completed Full Report

Efficacy	P05-03	5.3.5.1	To evaluate the effects of pitolisant on diurnal sleepiness in narcoleptic patients	Single blind, Sequential placebo-controlled	20 mg tablets Dose: 40 mg/day from Day 8 to Day 14 Oral route	22 (14M/8F)	Patients with narcolepsy	Repeated doses 14 days	Completed Full Report

Type of Study	Study Identifier	Location of Study Report	Main Objective of the Study	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Number of Subjects (#M/F)	Healthy Subjects or Diagnosis of Patients	Duration of Treatment	Study Status; Type of Report
Efficacy	P07-03	5.3.5.1	To evaluate the effects of pitolisant on excessive daytime sleepiness (EDS) in narcoleptic patients with or without cataplexy (HARMONY 1)	Randomized, double-blind, placebo-controlled, Active-controlled, parallel group	Tablets 20 mg Doses: 10 to 40 mg l/day Oral route	95 (51M/44F) Pitolisant (N=32) Placebo (N=30) Modafinil (N=33)	Patients with narcolepsy	Repeated doses 8 weeks	Completed Full Report
Efficacy	P07-07	5.3.5.1	To evaluate the effects of pitolisant on EDS in patients with narcolepsy and the additive effects in combination with Modafinil study (HARMONY II)	Randomized double-blind, parallel group	20 mg tablets Dose: 10 mg or 20 mg or 40 mg per day, placebo, or modafinil 200 mg/day Oral route	14 (8M/6F) Pitolisant + placebo (N=9) Pitolisant + Modafinil (N=5)	Patients with narcolepsy	Repeated doses 8 weeks	Completed Full Report

Efficacy	P09-15	5.3.5.1	To evaluate the effects of pitolisant on EDS in patients with or without cataplexy (HARMONY 1bis)	Randomized, double-blind, placebo-controlled, Active-controlled, parallel group	Tablets 20 mg Doses: 5 to 20 mg / day Oral route	165 (78M/88F) Pitolisant (N=67) Modafinil (N=65) Placebo (N=33)	Patients with narcolepsy	Repeated doses 8 weeks	Completed Full Report
Efficacy	P10-01	5.3.5.1	To evaluate the effects of pitolisant as add-on therapy to sodium oxybate on EDS and number of cataplexy crisis in patients with narcolepsy (HARMONY IV)	Randomized, double-blind, placebo-controlled,	Tablets 20 mg Dose: 10 to 40 mg per day Oral route	48 **(26)** (34M/14F) Pitolisant (N=26) Placebo (N=22)	Patients with narcolepsy	Repeated doses 8 weeks	Completed Full Report

Type of Study	Study Identifier	Location of Study Report	Main Objective of the Study	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Number of Subjects (#M/F)	Healthy Subjects or Diagnosis of Patients	Duration of Treatment	Study Status; Type of Report
Efficacy	P11-05	5.3.5.1	Effect on weekly cataplexy attacks (HARMONY CTP)	Randomized, double-blind, placebo-controlled, parallel group	Tablets 20 mg Dose: 5 to 40 mg per day Oral route	105 (53M/52F) Pitolisant (N=54) Placebo (N=51)	Patients with narcolepsy	Repeated doses 7 weeks	Completed Full Report
Efficacy	P11-06	5.3.5.1	Effect of pitolisant in reducing residual Excessive Daytime Sleepiness (EDS) and the number of cataplectic episodes (for	Randomized, double-blind, placebo-controlled, parallel group	Tablets 5 mg and 20 mg Dose: 5 to 40 mg per day Oral route	96 (NA)	Pediatric narcolepsy patients with or without cataplexy between 6 and 18 years	Repeated doses Double-blind: 8 weeks Open-label: long-term follow-up period until pitolisant is licensed for this age group.	Ongoing Not Applicable
Uncontrolled	P06-06	5.3.5.2	Initial tolerability narcolepsy	Open label	20 mg tablets Doses: 10 mg, 20 mg 40 mg/ day Oral route	26 (21M/5F)	Patients with narcolepsy	3 to 9 months	Completed Full Report

Uncontrolled	P09-10	5.3.5.2	To assess the long- term safety and maintenance of efficacy in narcoleptic patients (HARMONY III)	Open-label	Tablets 20 mg Dose: 5 to 40 mg per day Oral route	102 (45M/57F)	Patients with narcolepsy	Repeated doses 1 year Extension by amendment for French cohort up to 5 years	Completed Full Report

Type of Study	Study Identifier	Location of Study Report	Main Objective of the Study	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Number of Subjects (#M/F)	Healthy Subjects or Diagnosis of Patients	Duration of Treatment	Study Status; Type of Report
Uncontrolled	HBS-101-CL-001	5.3.5.2	To provide access to treatment with pitolisant to adult patients in the U.S. with EDS associated with narcolepsy, with or without cataplexy. To examine the safety and tolerability profile of pitolisant in adult patients with EDS associated with narcolepsy with or without cataplexy	Open-label, Extended Access Program for pitolisant	Pitolisant: Week 1: 10 mg/day Week 2: 20 mg/day Week 3: 40 mg/day Oral route	approximately 400 (planned) (NA)	Adult patients with narcolepsy (≥18 years)	Repeated doses up to 2 years	Ongoing Not Applicable
Other	P03-06	5.3.5.4	Action on photosensitivity in epileptic patients	Single blind	20 mg and 10 mg tablets Dose: 20 mg, 40 mg, 60 mg Oral	14 (12F/2M)	Patients with epilepsy	1 single dose	Completed Synopsis
Other	P04-01	5.3.5.4	Efficacy pilot of Pitolisant in Obstructive Sleep Apnea OSA, compared with	Single blind, Placebo-controlled sequential	20 mg tablets Dose: 40 mg at day 3, 4, 5; placebo at day 1, 2 and 6, 7 Oral route	12 (M)	Patients with moderate to severe OSA	Repeated doses 7 days	Completed Synopsis

Other	P04-07	5.3.5.4	Safety and effect in refractory partial seizures	Open label study using an exploratory approach	Tablets 20 mg Dose: 20 to 40 mg /day Oral route	23 (13M/10F)	Patients with partial seizure onset despite therapy	Repeated doses 3 months	Completed Synopsis

Type of Study	Study Identifier	Location of Study Report	Main Objective of the Study	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Number of Subjects (#M/F)	Healthy Subjects or Diagnosis of Patients	Duration of Treatment	Study Status; Type of Report
Other	P04-08	5.3.5.4	Efficacy and tolerance of pitolisant in Schizophrenia given alone or in combination with olanzapine versus olanzapine alone	Randomized, double-blind, placebo-controlled	Tablets 20 mg Doses: 40 mg/day Oral route	10 (5F/5M) Pitolisant (N=3) Olanzapine (N=4) Olanzapine + Pit (N=3)	Patients with schizophrenia	Repeated doses 3 months	Completed (study terminated early due to low recruitment) Synopsis
Other	P05-01	5.3.5.4	Exploratory study OSA	Single-blind, placebo-controlled sequential-	Tablets 20 mg Dose: 40 mg/ day Oral route	21 (M)	Patients with moderate to severe OSA (free of nCPAP)	Repeated doses 14 days	Completed Synopsis
Other	P05-05	5.3.5.4	Efficacy pilot in Parkinson	Single-blind, placebo-controlled, sequential study followed by optional open-label	Tablets 20 mg Dose: 40 mg /day Oral route	26 (20M/6F) N=26 (single-blind, sequential) N=18 (extension phase)	Patients with Parkinson's disease	Repeated doses 7 days Open label 3 months	Completed Synopsis

Other	P05-07	5.3.5.4	Efficacy and tolerance in ADHD	Single – blind, with an additional 8- week optional follow-up	Tablets 20 mg Doses: 10 mg, 20 mg, 40 mg /day Oral route	35 (17F/18M) Pitolisant (N=32) Placebo (N=3) Follow-up (N=13)	Patients with ADHD	Repeated doses 4 weeks Follow-up 8 weeks	Completed Synopsis

Type of Study	Study Identifier	Location of Study Report	Main Objective of the Study	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Number of Subjects (#M/F)	Healthy Subjects or Diagnosis of Patients	Duration of Treatment	Study Status; Type of Report
Other	P05-08	5.3.5.4	Efficacy on cognition, diurnal and nocturnal vigilance, hallucinations and other symptoms and tolerance in Lewy's body dementia (LBD)	Randomized, double-blind, placebo controlled, parallel group Extension phase	Tablets 20 mg Doses: 10 mg, 20 mg, 40 mg /day Oral route	37 (27M/9F) Pitolisant (N=19) Placebo (N=18) Extension phase (N=20)	Patients with Lewy's body dementia	Repeated doses 3 months Extension: 39 weeks	Completed Synopsis
Other	P06-10	5.3.5.4	Efficacy and safety in Parkinson patients (HARPS 1)	Randomized, double-blind, placebo-controlled, parallel group, with a 9-month extension	Tablets 20 mg Dose: 5 mg, 10 mg, 20 mg /day Oral route	235 (179M/56F) Pitolisant (N=151) Placebo (N=84) Open label	Patients with Parkinson's disease	Repeated doses 12 weeks Ext 9 months	Completed Synopsis
Other	P06-11	5.3.5.4	Efficacy and safety in Parkinson patients (HARPS 2)	Randomized, double-blind, placebo-controlled, parallel group, followed by a 9- month open-label	Tablets 20 mg Dose: 5 mg, 10 mg, 20 mg /day Oral route	231 (160M/71F) Pitolisant (N=159) Placebo (N=72) Open label	Patients with Parkinson's disease	Repeated doses 12 weeks Ext 9 months	Completed Synopsis

PK/tolerability	P07-02	5.3.5.4	Dose finding in Parkinson patients	Randomized, DB, placebo-controlled	20 mg tablets Doses: 5 mg, 10 mg, 20 mg, 40 mg / day placebo Oral	107 (78M/29F) Pitolisant (N=86) Placebo (N=21)	Patients with Parkinson's disease	Repeated doses 4 weeks	Completed Synopsis

Type of Study	Study Identifier	Location of Study Report	Main Objective of the Study	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Number of Subjects (#M/F)	Healthy Subjects or Diagnosis of Patients	Duration of Treatment	Study Status; Type of Report
Other	P09-08	5.3.5.4	Efficacy and safety in the treatment of Excessive Daytime Sleepiness in patients with OSA and treated	Prospective, randomized, double-blind study, placebo-controlled, parallel-group, multi-center study and 52-	Tablets 20 mg Dose: 5 to 20 mg per day Oral route	244 (183) (202M/42F)	Patients with OSA	Repeated doses 12 weeks Extension: 40 weeks	Completed Synopsis
Other	P09-09	5.3.5.4	Efficacy and safety in the treatment of Excessive Daytime Sleepiness in patients with OSA refusing	Prospective, randomized, double-blind study, placebo-controlled, parallel-group, multi-center study and 52-	Tablets 20 mg Dose: 5 to 20 mg per day Oral route	268 (202M/66F) Pitolisant (N=201) Placebo (N=67)	Patients with OSA	Repeated dose 12 weeks Extension: 40 weeks	Completed Synopsis
PK/tolerability	P09-16	5.3.5.4	Dose-finding study in moderate to severe OSA	Randomized, balanced, double-blind, parallel groups	Tablets 20 mg Dose: 5 mg, 10 mg, 20 mg, 40 mg/ day Oral route	116 (95M/11F) Pitolisant (N=91) Placebo (N=24)	Patients with OSA	Repeated doses 14 days	Completed Synopsis

Other	P14-08	5.3.5.4	Exploring Occupancy of the Histamine H3 Receptor by BF2.649 (Pitolisant) in Humans Using PET Scan	Prospective, single- center, placebo-controlled Within-subjects, single- blind, fixed-order drug schedule design	Tablets 40 mg Oral route	6 (NA)	Healthy Volunteers	Single dose	Completed Full Report

Type of Study	**Study Identifier**	**Location of Study Report**	**Main Objective of the Study**	**Study Design and Type of Control**	**Test Product(s); Dosage Regimen; Route of Administration**	**Number of Subjects (#M/F)**	**Healthy Subjects or Diagnosis of**	**Duration of Treatment**	**Study Status; Type of Report**
Other	P15-11	5.3.5.4	To collect information on the long-term safety of pitolisant (Wakix®) (all reported adverse	Observational post-authorization safety study	Tablets 5 mg and 20 mg Dose: 5 to 40 mg per day Oral route	300 (NA)	Adult patients with narcolepsy	Repeated doses 5 years	Ongoing Not Applicable
Other	P15-13	5.3.5.4	Efficacy and Safety in the treatment of Excessive Daytime Sleepiness in Patients with OSA (HAROSA III)	Prospective, multicenter, randomized, double blind, placebo-controlled, and 52-week open label extension phase	Tablets 5 mg and 20 mg Dose: 5 to 40 mg per day Oral route	180 (120) (NA)	Patients with OSA	Repeated dose 12 weeks	Ongoing Not Applicable

F = female; HV = healthy volunteer; M = male; NA = not available; Pit = pitolisant: PK = pharmacokinetic

13.4. Epworth Sleepiness Scale

Epworth Sleepiness Scale

Name:_____Today's date: _____

Your age (Yrs):_____Your sex (Male = M, Female = F): _____

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 haven't 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

It is important that you answer each question as best you can.

Situation	Chance of Dozing (0-3)
Sitting and reading	___
Watching TV	___
Sitting, inactive in a public place (e.g. a theatre 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	

THANK YOU FOR YOUR COOPERATION

13.5. Beck Depression Inventory – Short Form (BDI-SF)

BECK DEPRESSION INVENTORY, SHORT FORM

Instructions: This is a questionnaire. On the questionnaire are groups of statements. Please read the entire group of statements in each category. Then pick out the one statement in that group which best describes the way you feel today, that is, *right now*! Circle the number beside the statement you have chosen. If several statements in the group seem to apply equally well, circle each one.

Be sure to read all the statements in each group before making your choice.

A. (Sadness)
3 I am so sad or unhappy that I can't stand it.
2 I am blue or sad all the time and I can't snap out of it.
1 I feel sad or blue.
0 I do not feel sad.

B. (Pessimism)
3 I feel that the future is hopeless and that things cannot improve.
2 I feel I have nothing to look forward to.
1 I feel discouraged about the future.
0 I am not particularly pessimistic or discouraged about the future.

C. (Sense of failure)
3 I feel I am a complete failure as a person (parent, husband, wife).
2 As I look back on my life, all I can see is a lot of failures
1 I feel I have failed more than the average person.
0 I do not feel like a failure.

D. (Dissatisfaction)
3 I am dissatisfied with everything.
2 I don't get satisfaction out of anything anymore.
1 I don't enjoy things the way I used to.
0 I am not particularly dissatisfied.

E. (Guilt)
3 I feel as though I am very bad or worthless.
2 I feel quite guilty.
1 I feel bad or unworthy a good part of the time.
0 I don't feel particularly guilty.

F. (Self-dislike)
3 I hate myself.
2 I am disgusted with myself.
1 I am disappointed in myself.
0 I don't feel disappointed in myself.

G. (Self-harm)
3 I would kill myself if I had the chance.
2 I have definite plans about committing suicide.
1 I feel I would be better off dead.
0 I don't have any thoughts of harming myself.

H. (Social withdrawal)
3 I have lost all of my interest in other people and don't care about them at all.
2 I have lost most of my interest in other people and have little feeling for them.
1 I am less interested in other people than I used to be.
0 I have not lost interest in other people.

I. (Indecisiveness)
3 I can't make any decisions at all anymore.
2 I have great difficulty in making decisions.
1 I try to put off making decisions.
0 I make decisions about as well as ever.

J. (Self-image change)
3 I feel that I am ugly or repulsive-looking.
2 I feel that there are permanent changes in my appearance and they make me look unattractive.
1 I am worried that I am looking old or unattractive.
0 I don't feel that I look any worse than I used to.

K. (Work difficulty)
3 I can't do any work at all.
2 I have to push myself very hard to do anything.
1 It takes extra effort to get started at doing something.
0 I can work about as well as before.

L. (Fatigability)
3 I get too tired to do anything.
2 I get tired from doing anything.
1 I get tired more easily than I used to.
0 I don't get any more tired than usual.

M. (Anorexia)
3 I have no appetite at all anymore.
2 My appetite is much worse now.
1 My appetite is not as good as it used to be.
0 My appetite is no worse than usual.

13.6. Executive Summary and Relevant Tables, Pharmacovigilance Review – Division of Pharmacovigilance, Office of Surveillance and Epidemiology

The Division of Psychiatry Products (DPP) is reviewing a New Drug Application (NDA) for pitolisant, a histamine H-3-receptor (H3R) inverse agonist/antagonist that has been marketed in the European Union (EU) since 2016 for the treatment of excessive daytime sedation in patients with narcolepsy with or without cataplexy. To assist in their review of the application, DPP has requested that the Division of Pharmacovigilance (DPV) perform an analysis of EU postmarketing adverse event (AE) reports, as well as data from the sponsor's most recent (fourth) Periodic Benefit Risk Evaluation Report (PBRER-4).

DPV completed a high-level overview of postmarketing AE reports submitted to Vigibase and FAERS. We identified the most frequently reported Medical Dictionary for Regulatory Activities (MedDRA) Preferred Terms (PTs) but did not identify any new safety risks associated with pitolisant. Based on review of the PBRER and information provided by the European Medicines Agency (EMA), there have been no new risks identified for pitolisant in the postmarketing period, compared to the premarketing safety profile. The total postmarketing exposure for pitolisant has been low. During this reporting period, the sponsor has not taken or proposed any regulatory actions for safety reasons. They concluded that their review of the cumulative safety information obtained during the reporting period has not revealed any new major findings that impact the established overall safety profile of the product. Based on the information and analyses submitted by the sponsor, their conclusions seem reasonable. In the previous reporting period, the sponsor noted two cases of suicidal ideation and one case of mania in patients treated with pitolisant. They will perform cumulative reviews for these events.

The sponsor has provided an adequate summary and analysis of the relevant safety issues in PBRER-4. FDA continues to review the NDA for pitolisant. DPV has not identified any specific safety issues for further review. Currently, there are no safety issues that would require consideration of a risk evaluation or mitigation strategy (REMS).

Currently, DPV does not have specific regulatory recommendations for further safety analysis, enhanced pharmacovigilance, or postmarketing requirements or commitments. DPV will conduct routine pharmacovigilance regarding the safety issues that the sponsor has identified in their risk management plan and PBRER,

including suicidal ideation and behavior (SIB) and mania. We await the sponsor's cumulative analyses of events related to SIB and mania in the next PBRER.

Table 85: DPV Search Strategies - FAERS, Vigibase, EudraVigilance

FAERS Search Strategy	
Date of Search	March 6, 2019
Time Period of	All reports through March 5, 2019
Search Type	FBIS Quick Query
Product Terms	Product active ingredient: pitolisant, pitolisant
MedDRA Search Terms (Version	All adverse events
Vigibase Search Strategy	
Date of Search	March 8, 2019
Time Period of	All reports through March 3, 2019
Drug	Pitolisant (Substance)
MedDRA Search Terms (Version	All adverse events
EudraVigilance Search Strategy	
Date of Search	March 8, 2019
Time Period of	All reports through March 2019
Search Type	Suspected adverse drug reaction reports
Drug	Pitolisant (Substance)
Adverse Event	All adverse events

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

MARTINE M SOLAGES
08/14/2019 08:12:00 AM

BERNARD A FISCHER
08/14/2019 09:36:31 AM
Lead Medical Officer