CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

211150Orig2s000

STATISTICAL REVIEW(S)

M E M O R A N D U M DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: 8 June 2020

FROM: Semhar Ogbagaber, Ph.D.
Biometrics Reviewer
Division of Biometrics I
Office of Biostatistics

TO: **NDA 211150**/SDN 65 (Received on 10/25/2019): Type A NDA Post-Action Meeting Request and Briefing Document

SUBJECT: Resolve statistical method inconsistency between the SAP and CSR; WAKIX (Pitolisant) for Excessive daytime sleepiness (EDS) in adults with narcolepsy

Data Sources: \\CDSESUB1\evsprod\NDA211150\0005\m5\datasets (Data Sets in Original NDA Submission)
\\CDSESUB1\evsprod\NDA211150\0065 (Type A Meeting Material)
\\cdsesub1\evsprod\NDA211150\0030\m5\datasets\p07-03\analysis\adam\programs\fda011-harmony-i-cataplexy.txt (Information Request Response with SAS Code)

Pitolisant (trade name: Wakix) received EMA (European Medicines Agency) authorization on March 31, 2016 for the indication of excessive daytime sleepiness in narcolepsy with or without cataplexy. Narcolepsy is a serious, chronic, rare neurologic disorder characterized by excessive daytime sleepiness, cataplexy (sudden loss of muscle tone) and sleep paralysis.

The Applicant (Bioprojet Pharma) filed a New Drug Application (NDA 211150/Original 1 and NDA 211150/Original 2) to use Pitolisant for:

- Treatment of excessive daytime sleepiness (EDS) in adults with narcolepsy (supported by studies HARMONY 1, HARMONY 1BIS);
- Treatment of cataplexy in adults with narcolepsy (supported by study HARMONY CTP).

The Agency granted Orphan Drug Designation to pitolisant in March 2010. In April 2018, the cataplexy development program received Fast Track and Breakthrough Designation. Fast Track Designation was granted for the treatment of excessive daytime sleepiness (EDS) in narcolepsy, but Breakthrough Therapy Designation was denied.

Pitolisant received FDA approval for the treatment of EDS in adult patients with narcolepsy in August 2019. However, a Complete Response Letter (CRL) was issued for the cataplexy indication. The Applicant submitted two phase 3 studies in support of the cataplexy indication—HARMONY 1 and HARMONY CTP. As noted in the Complete Response Letter, the Agency determined that HARMONY 1 could not be considered as adequate and well-controlled trial for the cataplexy endpoint for the

following reasons:

1. Cataplexy was a secondary endpoint in HARMONY 1. There was no prospective plan to control the Type-I error rate for secondary endpoints in this study.
2. 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.
3. 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 only HARMONY CTP a positive, adequate, and well-controlled trial was submitted for the cataplexy indication. According to FDA Advice Letter, on June 15, 2011, a claim for anticataplectic activity needs to be substantiated by two adequate and well-controlled studies. In the same letter, FDA also advised on showing evidence of efficacy on both subjective and objective measures of sleepiness.

The Applicant requested a Type A Post-Action face to face meeting, for reconsideration of the CRL decision, and the meeting was held on December 12, 2019 to discuss the Applicant's re-analysis of the clinical data (number of cataplexy attacks) in HARMONY 1 using Poisson regression *which was specified in the original SAP* (November 28, 2010). It should be emphasized that although the SAP specified Poisson regression to analyze "number of cataplexy attacks", in all subsequent submissions including the package for Fast Track, Breakthrough and the NDA, the daily rate of cataplexy (DCR) was analyzed differently using geometric means (applying t-test). All results from the t-test were described in the EMA report, clinical study report (CSR) in the NDA submission.

In the meeting the Applicant highlighted with apology this inconsistency arose due to sponsor's statistician error. Subsequently, the Applicant made the case that, had Poisson regression been used and any post-hoc multiplicity adjustment procedure applied to all the secondary endpoints, then it can be argued a statistically significant cataplexy endpoint (daily cataplexy rate) can be added in the labeling.

Applicant's arguments made in the briefing package and during the meeting, showed the type 1 error was controlled for the cataplexy endpoint via an exhaustive list of multiplicity adjustment methods that were not pre-specified in the SAP. Thus, the Applicant asserted HARMONY 1 would be considered as the second adequate and well-controlled study to complement HARMONY CTP for the cataplexy indication. The Applicant vehemently agreed with the Agency about the need to prespecify primary and secondary endpoints along with multiplicity adjustment methods.

Following the post-action face-to-face meeting, the agency reviewed the briefing document and re-analyzed the cataplexy data in HARMONY 1 via Poisson regression as specified in the SAP. This statistical reviewer confirmed the sponsor's results supporting a statistically significant reduction in daily rate of cataplexy in the pitolisant group when compared with the placebo group.

During the review process, through information requests, the statistical reviewer found errors (in the estimated treatment effect, 95% CI) due to unwarranted use of wrong analysis set. Subsequently, the sponsor acknowledged the errors and rectified the

efficacy tables. This did not change the overall conclusion but took arduous effort from the statistical reviewer to make sure the sponsor presented accurate analysis results.

Based on consensus of the clinical team opinion, it accepts the subpopulation of any patient with a reported history of cataplexy (population [4] as defined in Appendix below) as satisfactory analysis set to study effect of pitolisant on cataplexy in HARMONY 1.

APPENDIX

Analysis Population	N	Cataplexy rR, 95% CI, p value	Mean Change Pitolisant	Mean Change Placebo
1-Full Analysis Set [a]	62	0.053 [0.009 ; 0.315], p=0.002	0.021	0.394
1-Full Analysis Set [b]	58	0.065 [0.012 ; 0.345], p=0.002	0.026	0.397
2-Cataplexy experienced during baseline	25	0.109 [0.024 ; 0.492], p=0.010	0.179	1.645
3-Cataplexy experienced during the whole trial	32	0.091 [0.020 ; 0.409], p=0.004	0.101	1.109
4-Cataplexy experience reported in the past	47	0.068 [0.013 ; 0.360], p=0.003	0.037	0.539

rR = rate ratio
N = sample size of each analysis population

The selection criteria for these populations remain identical to what was described in the Briefing Document:

1. The Full Analysis Set (FAS), also named the Extended Intent to Treat (EITT) population, includes all randomized patients, regardless of whether or not a patient experienced cataplexy; therefore, for some of these patients no cataplexy events were observed either during baseline or during the follow up. In this scenario, 62 patients are included in the analysis, with a rate ratio of 0.053 ([0.009, 0.315], p=0.002) (Full Analysis Set [a] in the table). To account for the patients with missing values (n=4) the analysis was also run using only the 58 patients without missing values (Full Analysis Set [b] in the table).
2. Cataplexy experienced during baseline includes all patients in the ITT population with cataplexy experienced during baseline. A rate ratio of 0.109 ([0.024; 0.492], p=0.010) was found, based on 25 patients.
3. Cataplexy experienced during the whole trial includes all patients who experienced at least one cataplexy event during either baseline or the follow up period. This is the population referred to by the Agency and, in agreement with the Agency, a rate ratio of 0.091 [0.020; 0.409], p=0.004 was found, based on 32 patients.
4. Cataplexy experience reported in the past includes all patients who reported a history of cataplexy before randomization. A rate ratio of 0.068 [0.013; 0.360], p=0.003 was found, based on 47 patients.

Source: Response to FDA Request for Information on 13 February 2020 via email to RPM ShinYe Chang. Sponsor's results were confirmed by the statistical reviewer.

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/

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U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Sciences
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA/BLA #:	211150/Original-1
Drug Name:	Pitolisant
Indication:	Excessive daytime sleepiness (EDS) in adults with narcolepsy, Cataplexy in adults with narcolepsy
Applicant:	Bioprojet Pharma
Date(s):	Submission Date: 12/14/2018 PDUFA Date: 08/14/2019
Review Priority:	Priority
Biometrics Division:	Division of Biometrics I
Statistical Reviewer:	Semhar Ogbagaber, Ph.D.
Concurring Reviewers:	Jinglin Zhong, Ph.D., HM James Hung, Ph.D.
Medical Division:	Division of Psychiatry Products
Clinical Team:	Martine Solages, M.D.
Project Manager:	Brendan Muoio, Pharm. D.

Table of Contents

LIST OF TABLES

LIST OF FIGURES

1 EXECUTIVE SUMMARY

Bioprojet Pharma submitted three primary efficacy studies (HARMONY 1, HARMONY 1BIS and HARMONY CTP) under NDA 211150 to investigate WAKIX (pitolisant) for two indications: 1) the treatment of excessive daytime sleepiness (EDS) in adults with narcolepsy (supported by HARMONY 1, HARMONY 1BIS); 2) the treatment of cataplexy in adults with narcolepsy (supported by HARMONY CTP). Narcolepsy is a serious, chronic, rare neurologic disorder characterized by excessive daytime sleepiness, cataplexy (sudden loss of muscle tone) and sleep paralysis. Pitolisant was approved by EMA (European Medicines Agency) for one indication, excessive daytime sleepiness in narcolepsy with or without cataplexy on March 31, 2016. The applicant provides only one study (HARMONY CTP) to support the cataplexy indication. According to FDA Advice Letter, on June 15, 2011, a claim for anticataplectic activity needs to be substantiated by two adequate and well-controlled studies. In the same letter, FDA also advised on showing evidence of efficacy on both subjective and objective measures of sleepiness.

The three studies evaluated flexible doses (as determined by investigators) of pitolisant versus placebo, that is, HARMONY 1 (10, 20, 40 mg/day), HARMONY CTP (5, 10, 20, 40 mg/day) and HARMONY 1BIS (5, 10, 20 mg/day).

Pitolisant treatment group showed statistically significant improvement in the primary efficacy endpoint, ESS (Epworth Sleepiness Scale) compared to placebo, in HARMONY 1 (LS mean difference = -3.10; $p = 0.02$) and HARMONY 1BIS (LS mean difference = -2.19; $p = 0.03$). The replicated efficacy results showed improved daytime sleepiness which supports the indication of EDS.

Pitolisant statistically significantly reduced risk of cataplectic events compared to placebo in HARMONY CTP (rate ratio: 0.51, $p < 0.0001$). The cataplectic claim is supported by results from HARMONY CTP and additional post-hoc analysis results on the daily rate of cataplexy (DRC) in HARMONY 1 on a subgroup of patients with a history of cataplexy. The Applicant generated supportive evidence from HARMONY 1; however, the analysis was post-hoc and the overall type 1 error rate was not controlled. In addition, this post-hoc analysis which is based on outcome-defined subgroups (exposed-population based on cataplexy events) violates the randomization principle and there is very likely to be imbalances in known and unknown covariates confounding the observed treatment differences. This may lead to invalid statistical comparisons. Thus, there appears to be only one successful trial supporting the indication of cataplexy.

All the studies were conducted outside of U.S. [HARMONY 1: mostly in Western Europe and 1 country in Central Europe; HARMONY CTP: Russia, Southeast, Central and Eastern Europe; HARMONY 1BIS: mostly Western Europe, 1 country in South America, 1 country in Central Europe].

2 INTRODUCTION

2.1 Overview

Pitolisant was approved by EMA (European Medicines Agency) for excessive daytime sleepiness and cataplexy associated with narcolepsy on March 31, 2016. The Applicant seeks to claim indication for excessive daytime sleepiness and cataplexy in patients with narcolepsy.

All the studies were conducted outside of US, in support of this NDA to evaluate the effect of pitolisant for treatment of excessive daytime sleepiness and cataplexy associated with narcolepsy.

Table 1: Summary of Trials to be Assessed in the Statistical Review

Trial ID	Design*	Treatment/ Sample Size	Endpoint/Analysis	Preliminary Findings
P07-03 (HARMONY 1)	Phase 3, multicenter, randomized, double-blind, placebo and comparator-controlled, parallel group study to evaluate BF2.649, for treatment of excessive daytime sleepiness (EDS) in narcoleptic patients with or without cataplexy	BF2.649 (10 to 40 mg/day) (31) Modafinil (100 to 400 mg/day) (33) Placebo (30)	Primary: Change from baseline to week 8 in Epworth Sleepiness Scale (ESS) total score. Note: Step-down approach was used to control for multiple comparisons of treatments: test superiority (BF2.649 > placebo) and non-inferiority (BF2.649 vs modafinil) on a fixed non-inferiority margin.	Primary: BF2.649 versus placebo is significant (p = 0.022). But, BF2.649 versus modafinil is not significant where 95% CI = (-2.11, 2.30) (p=0.932**). **Non-inferiority test couldn't be concluded, the 95% CI lower bound, -2.11 < non-inferiority margin NI=2).
P11-05 (HARMONY CTP)	Phase 3, multicenter, randomized, double-blind, placebo-controlled study to evaluate BF2.649, to decrease the frequency of cataplexy attacks and reduce excessive daytime sleepiness (EDS)	BF2.649 (5, 10, 20, 40 mg/day) (54) Placebo (51)	Primary: Weekly Rate of Cataplexy episodes (WRC); change in the average number of cataplexy attacks per week between the two weeks of baseline (Day -14 to Day 0) and the 4 weeks of stable treatment period (Day 21 to Day 49).	Primary: BF2.649 versus placebo is significant (p* < 0.0001). *Poisson regression adjusted for baseline

	in narcoleptic patients with cataplexy			
P09-15 (HARMONY 1BIS)	Phase 3, multicenter, randomized, double-blind, placebo and comparator-controlled, parallel group study to evaluate BF2.649, in the treatment of excessive daytime sleepiness (EDS) in narcolepsy	BF2.649 (5, 10, 20 mg/day) (66) Modafinil (100, 200, 400 mg/day) (65) Placebo (32)	Primary: Change from baseline to week 8 in Epworth Sleepiness Scale (ESS) total score. Note: Step-down approach was used to control for multiple comparisons of treatments: test superiority (BF2.649 > placebo) and non-inferiority (BF2.649 vs modafinil) on a fixed non-inferiority margin.	Primary: BF2.649 versus placebo is significant (p = 0.03). But, BF2.649 versus modafinil is not significant where 95% CI = (1.02, 4.48) (p=0.002**). **Non-inferiority test couldn't be concluded, the 95% CI lower bound, 1.02 < non-inferiority margin NI=2).

Source: Reviewer (there were no prospectively pre-specified key secondary endpoints in all three trials)

2.2 Data Sources

The sponsor's submitted data and SAS program listings for the two pivotal studies are available in the following directory of the CDER' electronic document room (EDR): \\Cdsesub1\evsprod\NDA211150\0005

3 STATISTICAL EVALUATION

3.1 Data and Analysis Quality

The reviewer found the quality and integrity of the submitted data satisfactory and acceptable for the review analysis.

3.2 Evaluation of Efficacy

The objective of these confirmatory studies was to provide evidence of efficacy of pitolisant for excessive daytime sleepiness and cataplexy in adult patients with narcolepsy.

3.2.1 Study Design and Endpoints

3.2.1.1 HARMONY 1

Study Design

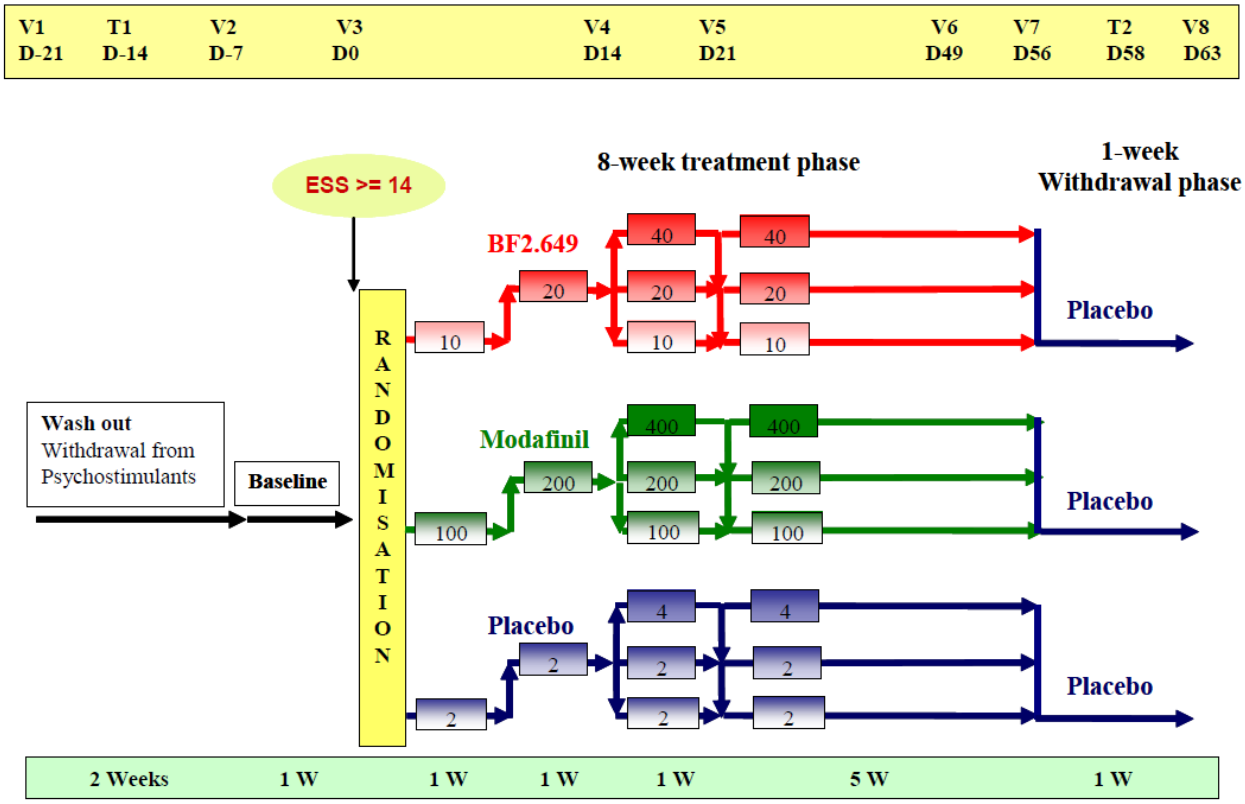
This is a phase 3, multicenter, randomized, double-blind, placebo and active-controlled (Modafinil), parallel group, flexible dose study. The study compares pitolis//ant (escalating doses of 10mg, 20mg or 40 mg) and Modafinil (escalating doses of 100mg, 200mg, or 400 mg) and placebo.

This study enrolled subjects at 24 centers in 5 countries: France, Germany, Hungary, the Netherlands and Switzerland. The first subject was enrolled on 26 May 2009 and the last subject's visit was on 30 June 2010. Subjects were 18 years of age or over and meet international classification of sleep for both new and previously diagnosed patients with narcolepsy with or without cataplexy.

If screened to enroll into the study, subjects would discontinue taking medications for EDS (such as modafinil, amphetamine or any other medications for treatment of EDS) during a washout period of at least 14 days prior to the baseline visit. If patients never used stimulants, they would enter the baseline period. However, cataplexy patients were allowed to remain on stable doses of anticataleptic medications (sodium oxybate, antidepressant such as SSRI) throughout the trial. Tricyclic antidepressants are prohibited.

During the baseline period, which lasted 7 days, patients were not allowed to take prohibited medications. Subjects who fulfilled the inclusion criteria (such as ESS at baseline ≥ 14) were randomized 1:1:1 to pitolisant, modafinil and placebo groups and enrolled in an 8-week double-blind treatment period. Randomized patients received flexible doses of pitolisant (10mg, 20mg, 40mg per day) and modafinil (100mg, 200mg, 400mg per day) with 3-week individual dose-titration period. Investigators were able to monitor and adjust doses during treatment period at days 0, 14, 21 based on individual response and tolerability. Subjects who completed the treatment period entered a 1-week withdrawal period during which all subjects received only placebo. The overall study period was 12 weeks.

Figure 1: Overall Study Schema-HARMONY 1



Source: Figure 1 of Sponsor's Clinical Study Report (Page 24)

Study Endpoints (Primary and secondary efficacy)

The primary efficacy outcome was the mean at the end of study ([V7+V6]/2) in ESS† (Epworth Somnolence Scale) total score between pitolisant and placebo. Higher scores of ESS total indicate increased sleepiness. The maximum total score is 24. Baseline ESS value (ESSBL) is measured at baseline visits, (V2 and V3). Final ESS value (ESSFINAL) is calculated as the arithmetic mean of V6 and V7, or the last visit for premature withdrawals (ESS*). ESS* is the value last observation carried forward. If no post-baseline value is available, then ESSFINAL = ESSBL.
Missing Baseline ESS: when ESS at V2 is missing then ESSBL will be calculated as the average at V1 and V3.

† ESS: *is a self-administered questionnaire which evaluates chances of dozing in eight different situations often encountered in daily life. Dozing probability ratings are "would never doze" (0 points), "slight chance of dozing" (1 point), moderate chance of dozing" (2 points), and "high chance of dozing" (3 points) in eight hypothetical situations often encountered in the daily life (CSR, page 36).*

Secondary endpoints: ESS responder rate (ESSF ≤ 10 or ESSF-ESSBL ≥ 3), Maintenance of Wakefulness Test (MWT), Daily Cataplexy Rate (DRC) and Sustained Attention to Response Task (SART).

The original protocol was issued on December 15, 2011, and was amended once on October, 2018.

Reviewer's Note 1: FDA Advice Letter on June 15, 2011 stipulated that anticataleptic activity claim should be supported by additional study as part of the two adequate and well-controlled studies for an indication.

Reviewer's Note 2: The sponsor conducted futility analysis "to avoid useless continuation of a trial" but the interim analysis had no impact on the overall trial plan.

3.2.1.2 HARMONY CTP

Study Design

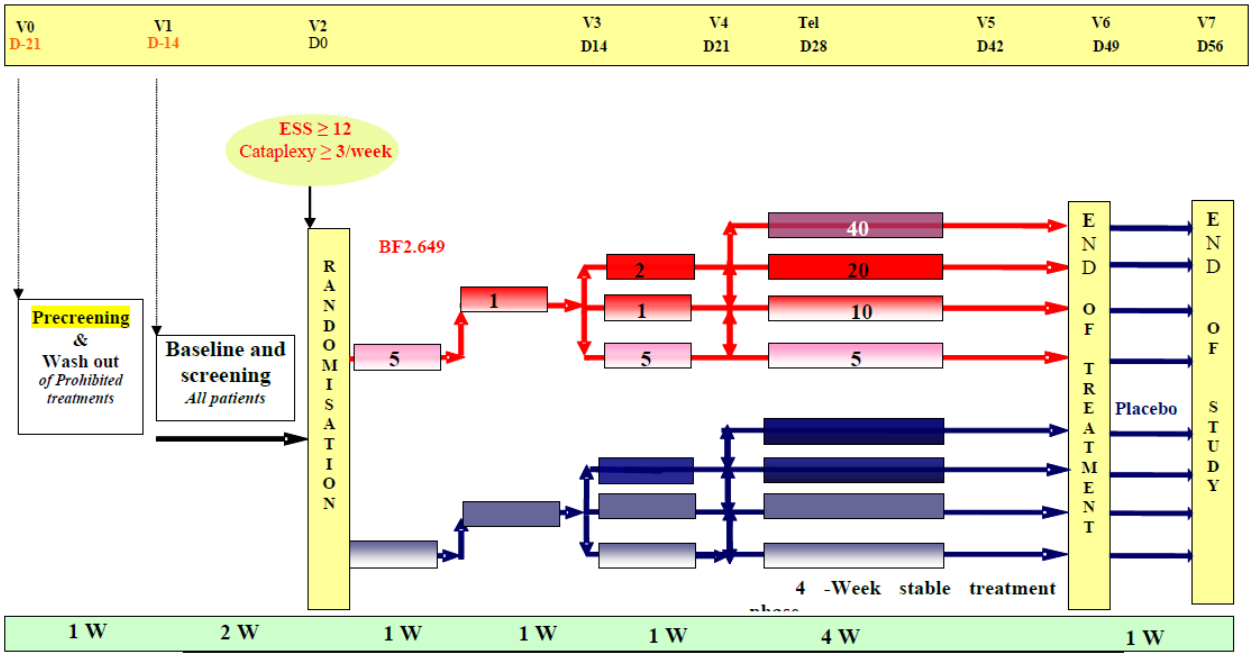
This is a phase 3, multicenter, double-blind, placebo -controlled, parallel group study to assess the effect of pitolisant (flexible doses: 5, 10, 20, 40 mg/day) on the weekly frequency of cataplexy attacks and on excessive daytime sleepiness in narcolepsy.

The trial was conducted at 16 centers in 9 countries: Bulgaria (1), Macedonia (1), Hungary (1), Serbia (1), Turkey (3), Czech Republic (1), Poland (2), Russia (5), Ukraine (1).

The study lasted from 19 April 2013 to 28 January 2015. The pre-screening and washout period lasted up to 1 week. During washout period patients who were on prohibited treatments (eg. psychostimulants) were discontinued. Eligible patients would then enter a 2-week baseline period. At baseline subjects were randomized (1:1) to pitolisant or placebo and will be treated for 7 weeks. The treatment period is split into 3-week individual dose-titration phase (Day 0 to 21). Once optimum dose was determined at V4 (Day 21), patients would receive treatment at this dose for 4 weeks (Day 21 to Day 49). At the end of treatment phase, study drug would be discontinued, and patients would receive placebo for 1 week (Day 49 to Day 56).

Diagnosis and Main Criteria for Inclusion: men and women aged 18 or above, diagnosis of narcolepsy with cataplexy (according to International Classification of Sleep Disorders, ICSD-2 criteria), "de-novo" patients or patients treated with purported anticataleptic drugs, i.e., SSRIs and sodium oxybate at stable dose for a minimum of one month and shown incidence of at least 3 weekly cataplexy attacks with excessive daytime sleepiness of ESS score ≥ 12.

Figure 2: Overall Study Schema-HARMONY CTP



Source: Figure 9.1:1 of Sponsor's Clinical Study Report (Page 32)

Study Endpoints (Primary and Secondary efficacy)

The primary efficacy outcome was the change in the average number of cataplexy attacks per week between the 2 weeks of baseline and the 4 weeks of stable dose period. This endpoint was retrieved from patient diaries.

Secondary endpoints: cataplexy rate during the last 2 weeks of treatment, MWT.

The original protocol which was issued on 30 July 2012 was amended once on 29 October 2012.

3.2.1.3 HARMONY 1BIS

Study Design

This is a randomized, double-blind, placebo and Modafinil controlled, parallel group, multicenter trial assessing the effects of pitolisant in the treatment of excessive daytime sleepiness in narcolepsy. The study compares pitolisant (escalating doses of 5mg, 10mg or 20 mg) and Modafinil (escalating doses of 100mg, 200mg, or 400 mg) and placebo.

This study was multinational and multicenter in scope: 32 study sites and 8 countries: Argentina (2 sites), Austria (1 site), Finland (1 site), France (8 sites), Germany (4 sites), Hungary (4 sites), Italy (6 sites), Spain (6 sites). The first subject was enrolled on 25 October 2010 and the last subject's visit was on 24 July 2012.

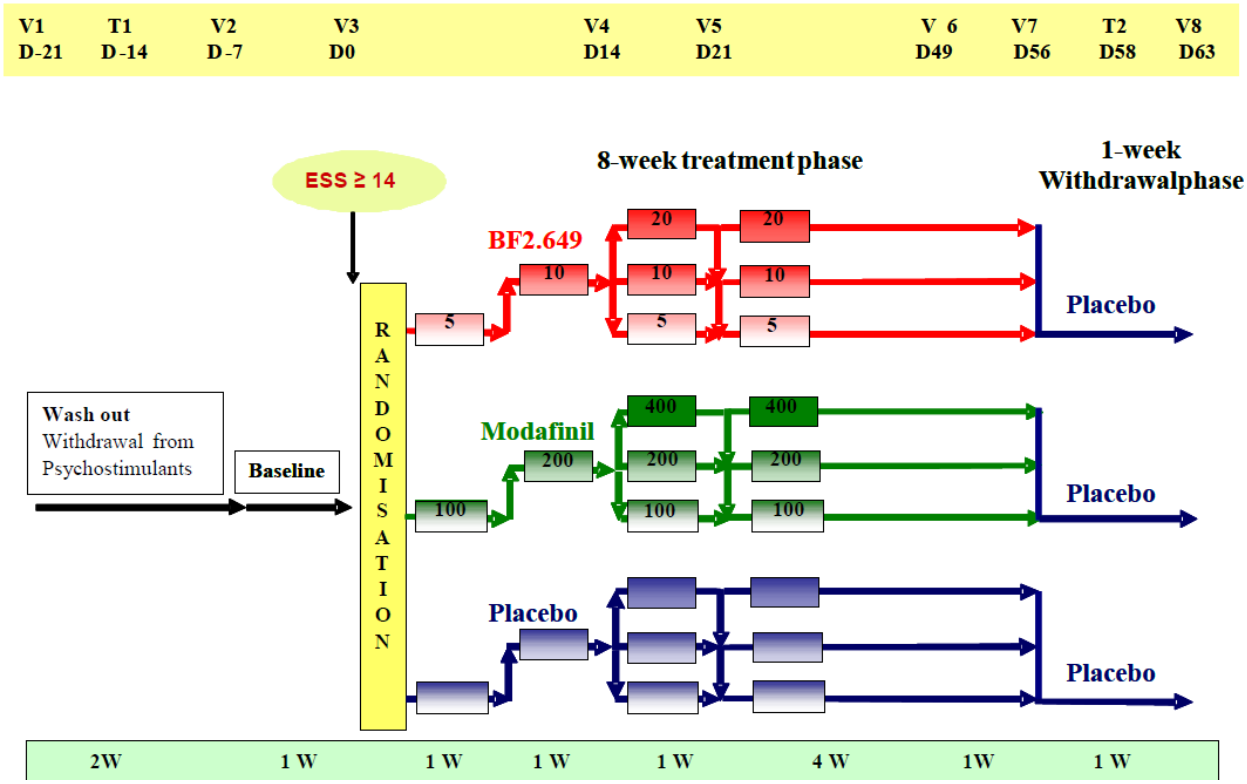
Diagnosis and Main Criteria for Inclusion: Subjects were 18 years of age or over; male or female; diagnosed with narcolepsy with or without cataplexy and meet the International Classification of Sleep Disorders (ICSD-2) criteria.

After 2 weeks of washout period during which they discontinue taking prohibited medications such as psychostimulants, baseline measures were taken during the 1-week baseline period. If patients never used stimulants, they would enter the baseline period. Total duration of the trial, from screening visit (V1) to final visit (V8), was 12 weeks: a 2-week washout period (V1 to V2), 1-week baseline period (V2-V3), an 8-week treatment period (V3-V7) and a 1-week withdrawal phase (V7-V8).

Subjects who fulfilled the inclusion criteria (such as ESS at baseline $\geq$ 14) were randomized* 2:2:1 to pitolisant, modafinil and placebo groups and enrolled in an 8-week double-blind treatment period. From D1 to D7, patients received BF2.649 5 mg/d or modafinil 100 mg/d or placebo. From D8 to D14, doses were increased to pitolisant (10 mg/day), modafinil (200 mg/day) or placebo. At D15, doses could be adjusted according to individual benefit/risk ratio (5, 10 or 20 mg/day for pitolisant; 100, 200 or 400 mg/day for modafinil; placebo). At D21, an individual dose adjustment could be performed again, but no dose increase was allowed. Dose remained stable for a five-week period and all patients received placebo in the subsequent 1-week withdrawal period (D56 to D63).

*Unequal Randomization: According to applicant's stated rationale, the choice of unequal randomization was for two reasons: to test for both superiority and inferiority, and safety. That is, *"The choice of an initial 1:2:2 randomization ratio was: a) this was together a superiority test (Placebo><verum), and a non-inferiority test (verum><modafinil). However the non-inferiority test obviously requires more patients, thus the size of the placebo arm might be reduced, b) the decision to increase the two verum arms was for safety purposes."* (CSR, page 26)

Figure 3: Overall Study Schema-HARMONY 1BIS



Source: Figure 1 of Sponsor's Clinical Study Report (Page 24)

Study Endpoints (Primary and secondary efficacy)

The primary efficacy outcome was the mean difference of ESS total score at final visit ([V7+V6]/2) between pitolisant and placebo. Higher scores of ESS total indicate increased sleepiness. The maximum total score is 24. Baseline ESS value (ESSBL) is measured at baseline visits, (V2 and V3). Final ESS value (ESSFINAL) is calculated as the arithmetic mean of V6 and V7, or the last visit for premature withdrawals (ESS*). ESS* is the summary mean of the two last observation carried forward values. If no post-baseline value is available, then ESSFINAL = ESSBL.

Missing Baseline ESS: when ESS at V2 is missing then ESSBL will be calculated as the average at V1 and V3.

Secondary endpoints: ESS responder rate (ESSF $\leq$ 10 or ESSF-ESSBL $\geq$ 3), daily cataplexy rate, MWT, SART.

The original protocol which was issued on 30 April 2010 and all changes including a sample size increase was amended on 26 April 2011.

3.2.2 Statistical Methodologies

The following statistical methodologies were pre-specified in the sponsor's statistical analysis plan.

3.2.2.1 HARMONY 1

The primary analysis for the primary and other secondary efficacy endpoints was carried out on the intention to treat (ITT). The ITT population included all randomized patients who received at least 1 dose of study medication and provided at least 1 post-baseline value.

Efficacy Analyses Methods (Primary Efficacy)

The comparison between potosilant and placebo for ESS final score (ESSF) was analyzed using analysis of covariance with linear mixed effect model, adjusted for ESS baseline score (ESSBL), treatment (fixed effect) and center (random effect). The final visit scores were imputed using last observation carried forward (LOCF). The difference in ESS final scores between pitolisant and modafinil was assessed if there was a statistically significant difference between pitolisant and placebo groups.

Multiple Comparisons: step-down approach was conducted to control type 1 error rate. The 2 hypotheses, superiority (pitolisant > placebo) and non-inferiority (pitolisant vs modafinil) on a fixed non-inferiority margin (NIM), were tested on the same alpha level (0.025). That is,
Step 1: H_{01}: pitolisant $\leq$ placebo must be rejected at $\alpha = 0.025$. Proceed to test H_{02} when H_{01} was rejected.
Step 2: H_{02}: pitolisant $\leq$ modafinil $- \theta$ (where θ=2 is the NIM) must be rejected at $\alpha = 0.025$.

Efficacy Analyses Methods (Other Efficacy Endpoints)

The effect of pitolisant group was assessed based on ESS responder rate (logistic regression); geometric mean ratio based on pooled Student t-test for Maintenance of Wakefulness Test (MWT) Sustained Attention to Response Task (SART) and Daily Cataplectic Rate. The last observed value is imputed in a similar manner as the primary efficacy endpoint.

Both MWT and SART were administered, in four sessions, at visit 3 and end of treatment period (visit 8). During a 40-minute session, MWT measures ability to stay awake in minutes. The SART (a complete assessment takes 4 min, 20 sec), used to quantify vigilance and attention in narcolepsy patients, consists of 3 error measurement scores: "the number of times a key is pressed when 3 is presented" ("NO GO"), "the number of times when no key is pressed when it should have been" ("GO"), and the sum of the two components.

Multiplicity: In testing the secondary endpoints, there were no corrections made for multiplicity to control the overall type I error rate.

Reviewer's Note: According to sponsor's SAP (November 28, 2010), the secondary endpoints, MWT and SART, were to be assessed according to a non-parametric Mann-Whitney test since they were not assumed to follow normal distribution. But this non-parametric method was not utilized in the final data analysis.

In response to FDA Information Request on 27 March 2019, the Applicant conducted analyses based on Mann-Whitney test for the secondary endpoint: MWT. See Reviewer Comment 1 in Section 3.2.2.1 whether the specified confirmatory results for MWT remained consistent.

Sensitivity Analyses

- Primary efficacy analysis on PP (per-protocol) population.

Supportive Analyses

A few ANCOVA without center effect were computed:

1. ESSF adjusted on ESSBL
2. ESSF not adjusted on ESSBL

3.2.2.2 HARMONY CTP

The primary analysis (for the primary and secondary endpoints) was carried out on the intent-to-treat (ITT) population. The ITT included all randomized patients who received at least 1 dose and have at least 1 post-dose value to compute the primary endpoint.

Efficacy Analyses Methods (Primary Efficacy)

The effect of pitolisant was compared to placebo using a mixed non-linear model where weekly rate of cataplexies (WRC) was assumed to follow Poisson distribution. Efficacy between treatment groups was assessed using the change in the average number of cataplexy attacks per week between the 2 weeks of baseline (Day -14 to Day 0) and the 4 weeks of stable treatment period (Day 21 to Day 49). The model was adjusted for baseline WRC, treatment as a fixed factor and center as random effect was included to account for heterogeneity.

Efficacy Analyses Methods (Secondary Efficacy)

The geometric mean of the weekly rate of cataplexies (WRC >= 0) on the two last final weeks of treatment period was compared to the baseline. Estimated mean of baseline include mean of week 1 and week 2; estimated mean of final two weeks of stable treatment period include week 8 (Day 42) and week 9 (Day 49). A similar mixed non-linear model featuring Poisson distribution (for WRC) and taking into account center heterogeneity was conducted.
MWT was analyzed using geometric mean (via pooled Student t-test).

Multiplicity: Multiple testing was not considered because the secondary endpoints were deemed as supportive or hypothesis generating.

Sensitivity Analyses

Due to possible over-dispersion of WRC, Quasi Poisson regression model and a negative binomial regression model were fitted.

3.2.2.3 HARMONY 1BIS

The primary efficacy was conducted on the FAS population. The FAS includes subjects who were randomized, received at least 1 dose of study drug, and had at least 1 valid post-baseline value for assessment of primary efficacy.

Efficacy Analyses Methods (Primary Efficacy)

The primary analysis method for the final ESS score (ESSF) was a linear mixed effect model (LME), which included baseline ESS score (ESSBL), treatment as a fixed effect and center as a

random effect. The hypothesis testing involved a superiority (vs. placebo) and non-inferiority (vs. modafinil) test of pitolisant. The non-inferiority test was based on the non-inferiority margin of -2.

Efficacy Analyses Methods (Other Efficacy Endpoints)
Logistic regression for ESS responder rate*; linear fixed effect model for Maintenance of Wakefulness Test (MWT) and Sustained Attention to Response Task (SART); quasi-Poisson regression model for daily cataplexy rates (DCR).

* ESS responder rate: defined as the absolute value of ESSF $\leq$ 10 at study end or ESSF – ESSBL > 3.

Multiplicity: In testing the secondary endpoints, there were no corrections made for multiplicity to control the overall type I error rate.

However, a step-down approach was used to test superiority (pitolisant > placebo) and non-inferiority (pitolisant vs modafinil) on a fixed non-inferiority margin (NIM).

Sensitivity Analyses

- Primary efficacy analysis on PP (per-protocol) population.

Supportive Analyses

A few ANCOVA without center effect were computed:

3. ESSF adjusted on ESSBL
4. ESSF not adjusted on ESSBL

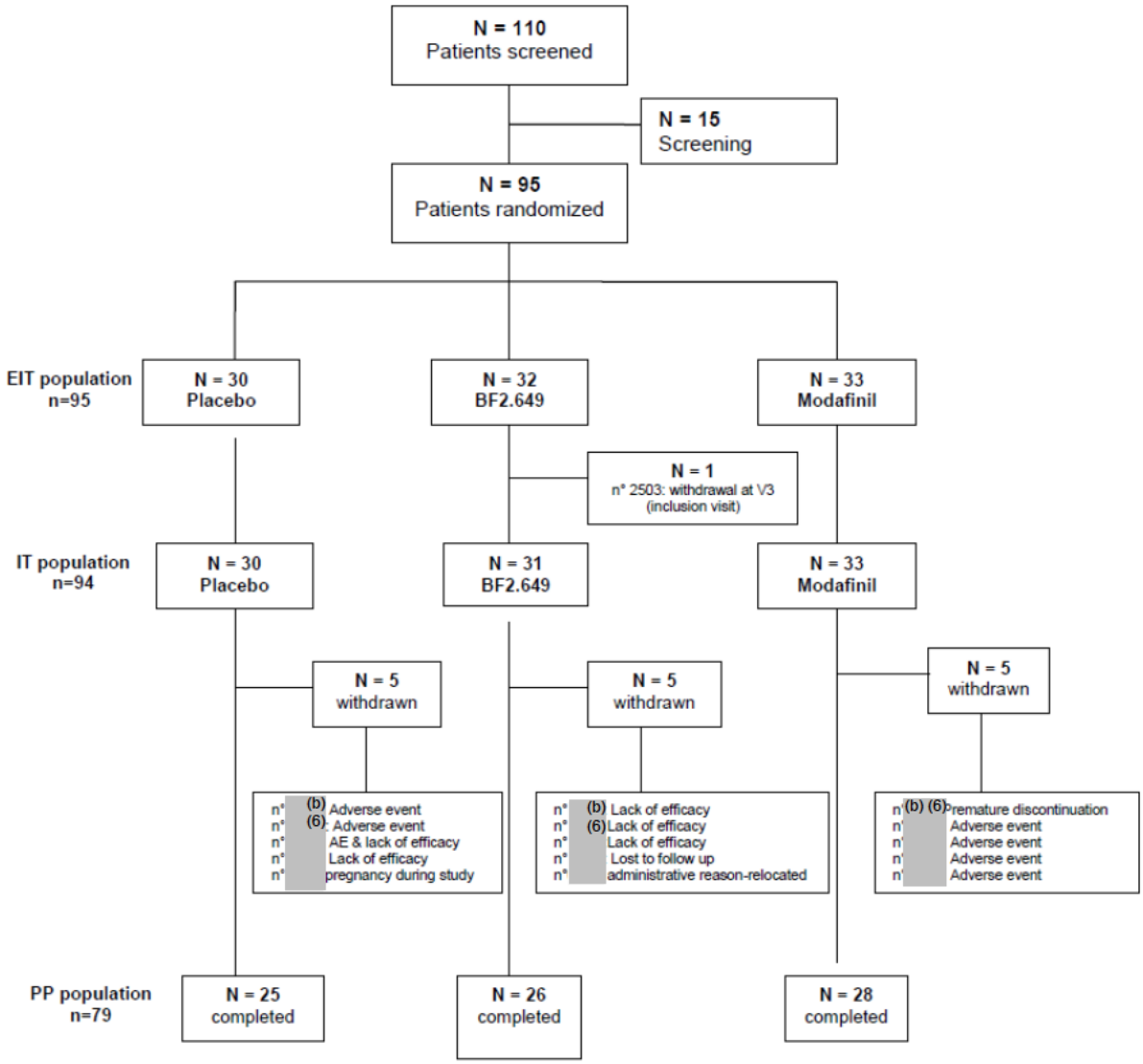
3.2.3 Patient Disposition, Demographic and Baseline Characteristics

3.2.3.1 HARMONY 1

Of the 110 patients screened, 95 subjects met the eligibility criteria and were randomized placebo (30), pitolisant (32), or modafinil (33). The ITT included 94 patients since one subject has no post-baseline measurements.

Table 1 and Figure 4 display overall subject dispositions, including the percentage of discontinuation for all randomized subjects in the 3 treatment groups due to major or premature withdrawals: placebo (16.7%), pitolisant (16.1%), modafinil (15.2%), which was similar across treatment groups. Overall discontinuation rate was 15.2%. The frequent discontinuation reasons included adverse events (8.5%) and lack of efficacy (4.3%).

Figure 4: Patient Disposition-HARMONY 1



Source: Figure 3 of Sponsor's Clinical Study Report (Page 53)

Table 2: Disposition of Patients-HARMONY 1 [n (%)] (All Patients)

	PLACEBO	BF2.649	MODAFINIL	ALL
Selected	-	-	-	110
Randomized / Extended Intent-to-treat (EIT)	30	32	33	95 (100%)
Randomized / Intent-to-treat (IT)	30 (31.9%)	31 (33%) *	33 (35.1%)	94 (100%)
Major deviations or Premature Withdrawals	5 (16.7%)	5 (16.1%)	5 (15.2%)	15 (16%)
Per Protocol (PP)	25 (31.6%)	26 (32.9%)	28 (35.4%)	79 (100%)
Completed	25 (31.6%)	26 (32.9%)	28 (35.4%)	79 (100%)
Premature Withdrawals	5 (16.7%)	5 (16.1%)	5 (15.2%)	15 (16%)
Minor deviations	25 (83.3%)	29 (93.5%)	24 (72.7%)	78 (83%)
** Patient (b) (6) was excluded from IT population due to consent withdrawal.* *Analysis was conducted on ADSL and ADDV datasets*				

Source: Table 14.1.1.1 in Appendix 14 of Sponsor's Clinical Study Report (Page 6)

Baseline demographic characteristics were balanced across the randomized population as summarized in Table 2. The average age of patients was 39 years ranging from 18 to 75 years; majority of participants were whites (94.7%). Also, the baseline narcolepsy characteristics were similar across the three treatment groups (Table 3).

Table 3: Summary of Demographic Characteristics-HARMONY 1 (ITT Population)

	PLACEBO (N=30)		BF2.649 (N=31)		MODAFINIL (N=33)		p-value
Parameter	**N**	**Value[1]**	**N**	**Value[1]**	**N**	**Value[1]**	
Age (yr)	30	39.5 [30.0; 52.0]	31	33.0 [21.0; 49.0]	33	40.0 [2.05; 48.0]	0.335
Weight (kg)	30	81.0 ± 20.7	31	90.9 ± 21.0	33	81.0 ± 16.3	0.073
Height (cm)	30	168.8 ± 10.4	31	173.9 ± 9.8	33	171.0 ± 8.5	0.122
BMI (kg/m²)	30	28.2 ± 6.0	31	30.4 ± 8.3	33	27.7 ± 5.3	0.250
Gender (Males)	30	43.3 (13)	31	64.5 (20)	33	54.5 (18)	0.274
2 yrs Post-Menopause or Sterilized	17	35.3 (6)	11	27.3 (3)	15	26.7 (4)	0.916
Mode of Contraception[2]	11		8		11		
Bill Control Pill		18.2 (2)		37.5 (3)		18.2 (2)	0.880
IUD		27.3 (3)		12.5 (1)		18.2 (2)	
Other Method		54.5 (6)		50.0 (4)		63.6 (7)	
Race	30		31		33		
White		93.3 (28)		93.5 (29)		97.0 (32)	0.736
Black or African American		6.7 (2)		6.5 (2)		3.0 (1)	

Source: Table 6 of Sponsor's Clinical Study Report (Ref. 14.1.2.1, Page 56)

[1]Data are expressed as Mean ± SD for weight, height, BMI; as % (n) for gender, contraception, race; as Median [25th%; 75th%] for age.

[2] Patient (b) (6) birth control method by vaginal route equivalent to 0.03 mg ethinyl estradiol by oral route; Patients (b) (6) were using oral estroprogestative as birth control method with a dose different to 0.05 mg of ethinylestradiol. These three deviations were considered minor.

Table 4: Summary of Baseline Narcolepsy Characteristics-HARMONY 1 (ITT Population)

	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

Source: Table 7 of Sponsor's Clinical Study Report (Ref: Table 14.1.2.1, Page 57)

[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.

3.2.3.2 HARMONY CTP

Of 117 subjects who were selected, 106 subjects were randomized. The ITT set included 106 subjects (51 subjects in placebo group and 54 subjects in pitolisant group).

Table 5: Disposition of Patients-HARMONY CTP [% (n/N)]

Patient Status	PLACEBO N	BF2.649 N	TOTAL N
Selected			117
Randomized	52	54	106
Safety (SAF)[1]	51	54	105
Intent-to-Treat (IT)	51	54	105
Per Protocol (PP)[2]	42	49	91
Number of Patients who Completed Study	48	50	98
Number of Patients with Major Deviations	6	1	7
Number of Patients with Premature Withdrawal[3]	3	4	7
Number of Patients with Minor Deviations	28	26	54

[1] Patient (b) (6) in the placebo group prematurely withdrew the study on his own decision the day after randomization before first treatment intake and was excluded from Safety Population

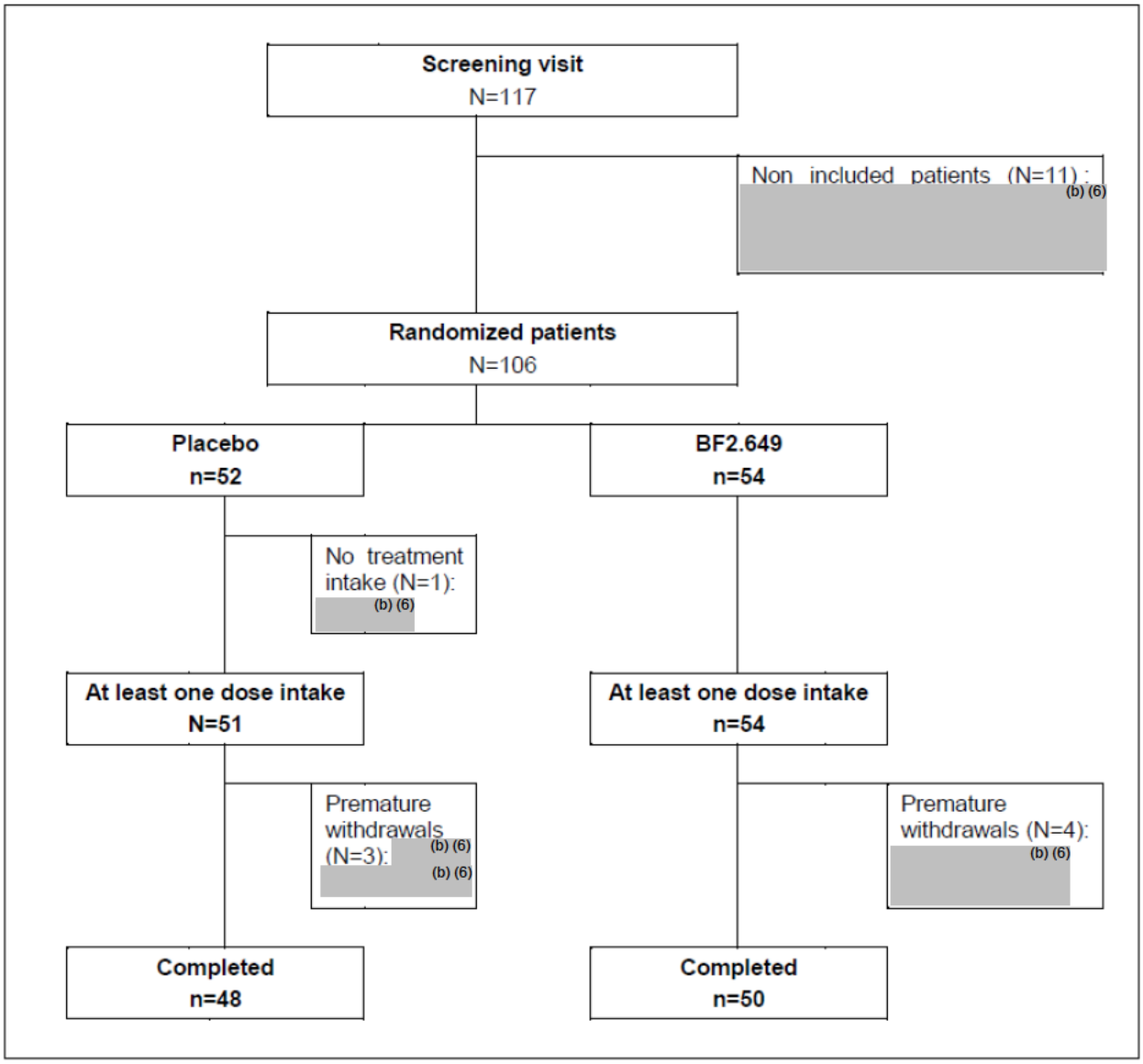
[2] Fourteen patients of IT population were excluded from the PP population: 7 patients with premature withdrawal (b) (6) (b) (6) and 7 patients with major protocol deviation ((b) (6) (b) (6)

[3] Premature withdrawals among patients who took at least one dose of study drug, i.e. excluding patient (b) (6) who was prematurely withdrawn without having any dose.

Source: Table 10.1-1 of Sponsor's Clinical Study Report (Page 72)

Figure 5 below shows that 98 (92.4%) subjects who completed the study (48 (94.1%) in the placebo arm; 50 (92.6%) in pitolisant arm). Seven (7) subjects (6.7%) prematurely discontinued the study: 6 (12.5% subjects in the placebo arm; 1 (2.0%) subjects in pitolisant arm). The most common reason for premature withdrawal [6 (85.7%)] was due to patient's decision alone.

Figure 5: Patient Disposition Schematic-HARMONY CTP



Source: Figure 10.1:1 of Sponsor's Clinical Study Report (Page 74)

The demographic characteristics in the randomized set are presented in Table 5. All patients are below the age of 64 years except one in placebo group. The average age of patients was 38.8 years in placebo and 35.8 years in pitolisant. All participants were white.

Table 6: Summary of Demographics and Baseline Characteristics-HARMONY CTP (ITT Population)

		PLACEBO (N=51)		BF2.649 (N=54)		
Parameter		**n**	**MN ± SD Or % (n/N)**	**n**	**MN ± SD % (n/N)**	**P-value**
Age	(median ; [min max])	51	39 [18; 66]	54	34 [18; 64]	0.232
< 65 yrs	(% (n/N)	.	98.0 (50/51)	.	100.0 (54/54)	0.301
[65 – 74] yrs	(% (n/N)	.	2.0 (1/51)	.	0.0 (0/54)	
Gender						
Male	(% (n/N)	.	52.9 (27/51)	.	48.1 (26/54)	0.623
Female	(% (n/N)	.	47.1 (24/51)	.	51.9 (28/54)	
Weight (kg)	(Mean±SD)	51	85 ± 18.3	54	80.1 ± 17.8	0.164
Height (cm)	(% (n/N)	51	172 ± 10.7	54	171.4 ± 9.1	0.738
BMI		51	28.8 ± 6.0	54	27.2 ± 5.2	0.144
Female						
Sterilized or 2-years post menopausal females	(% (n/N)	.	45.8 (11/24)	.	17.9 (5/28)	0.029
Mode of Contraception						
Oestroprogestive	(% (n/N)	.	53.8 (7/13)	.	34.8 (8/23)	0.605
IUD	(% (n/N)	.	7.7 (1/13)	.	8.7 (2/23)	
Other method	(% (n/N)	.	38.5 (5/13)	.	56.5 (13/23)	
SBP at V1	(Mean±SD)	51	122.2 ± 10.9	54	122.1 ± 11.7	0.976
DBP at V1		51	77.3 ± 7.5	54	77.6 ± 9.1	0.883
HR atV1		51	72.3 ± 9.6	54	72.1 ± 10.2	0.902
ECG at baseline	(Mean±SD)					
HR		51	68.3 ± 10.9	54	66.8 ± 11.3	0.507
PR		51	153.5 ± 33	54	164.2 ± 30.8	0.086
QRS		51	89.1 ± 14.3	54	86.6 ± 13.5	0.350
QT		51	387.5 ± 32.5	54	382.6 ± 35.9	0.464
QTcF		51	403.7 ± 29.7	54	395.9 ± 34.2	0.215
Rythm sinus - Abnormal		51	0.0 (0/51)	54	1.9 (1/54)	0.329
Rythm sinus – Normal		51	100.0 (51/51)	54	98.1 (53/54)	0.329

Source: Summary of Demographics of Sponsor's CSR (Table 11.2-1, Page 79)
MN=Mean; SD=standard deviation

Baseline score characteristics of narcolepsy and cataplexy (Table 6) were similar across the treatment groups. There was no considerable difference in the number of cataplexy episodes and history of associated symptoms between treatment groups.

Table 7: Summary of Baseline Narcolepsy and Cataplexy Characteristics-HARMONY CTP [Mean +/- SD; %(n/N)] (ITT Population)

	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: Summary of Baseline Characteristics of Sponsor's CSR (Table 11.2-2, Page 80)
SD=standard deviation

3.2.3.3 HARMONY 1BIS

Of the 183 patients who were selected, 166 were randomized of which 163 were included in the ITT population: placebo (32), pitolisant (66), or modanifil (65). Three (3) patients were excluded from the randomized population which formed the ITT for the following reasons: never took the study drug (modafinil), diagnosis of narcolepsy was not confirmed (placebo), only took one dose of treatment (pitolisant).

Table 8: Disposition of Patients-HARMONY 1BIS [% (n)]

Patient Status	PLACEBO % (n)	BF2.649 % (n)	MODAFINIL % (n)	TOTAL N
Selected	-	-	-	**183**
Randomized	**19.9 (33)**	**40.4 (67)**	**39.8 (66)**	**166**
Safety[1]	**20.0 (33)**	**40.6 (67)**	**39.4 (65)**	**165**
Extended Intent-to-Treat (EIT)[2]	**19.5 (32)**	**40.9 (67)**	**39.6 (65)**	**164**
Intent-to-Treat (ITT)[3]	**19.6 (32)**	**40.5 (66)**	**39.9 (65)**	**163**
Major Deviations	0.0 (0)	0.0 (0)	1.5% (1)	1
Per Protocol (PP)[4]	**19.7 (30)**	**39.5 (60)**	**40.8 (62)**	**152**
Completed	20.3 (31)	39.2 (60)	40.5 (62)	153
Premature Withdrawals[5]	16.7 (2)	58.3 (7)	25.0 (3)	12
Minor Deviations	44.4 (4)	44.4 (4)	11.1 (1)	9

[1] Patient (b) (6) was prematurely withdrawn after randomization before first treatment intake and was excluded from Safety Population

[2] Patient (b) (6) did not meet criteria for a diagnosis of narcolepsy and was excluded from the efficacy analysis but taken into account for the analysis of safety as he/she had received the study treatment; this patient prematurely discontinued the study treatment but was not prematurely withdrawn from the trial and was considered as completed the study.

[3] Patient (b) (6) had premature withdrawal at D14 after only one treatment intake and was excluded from ITT population.

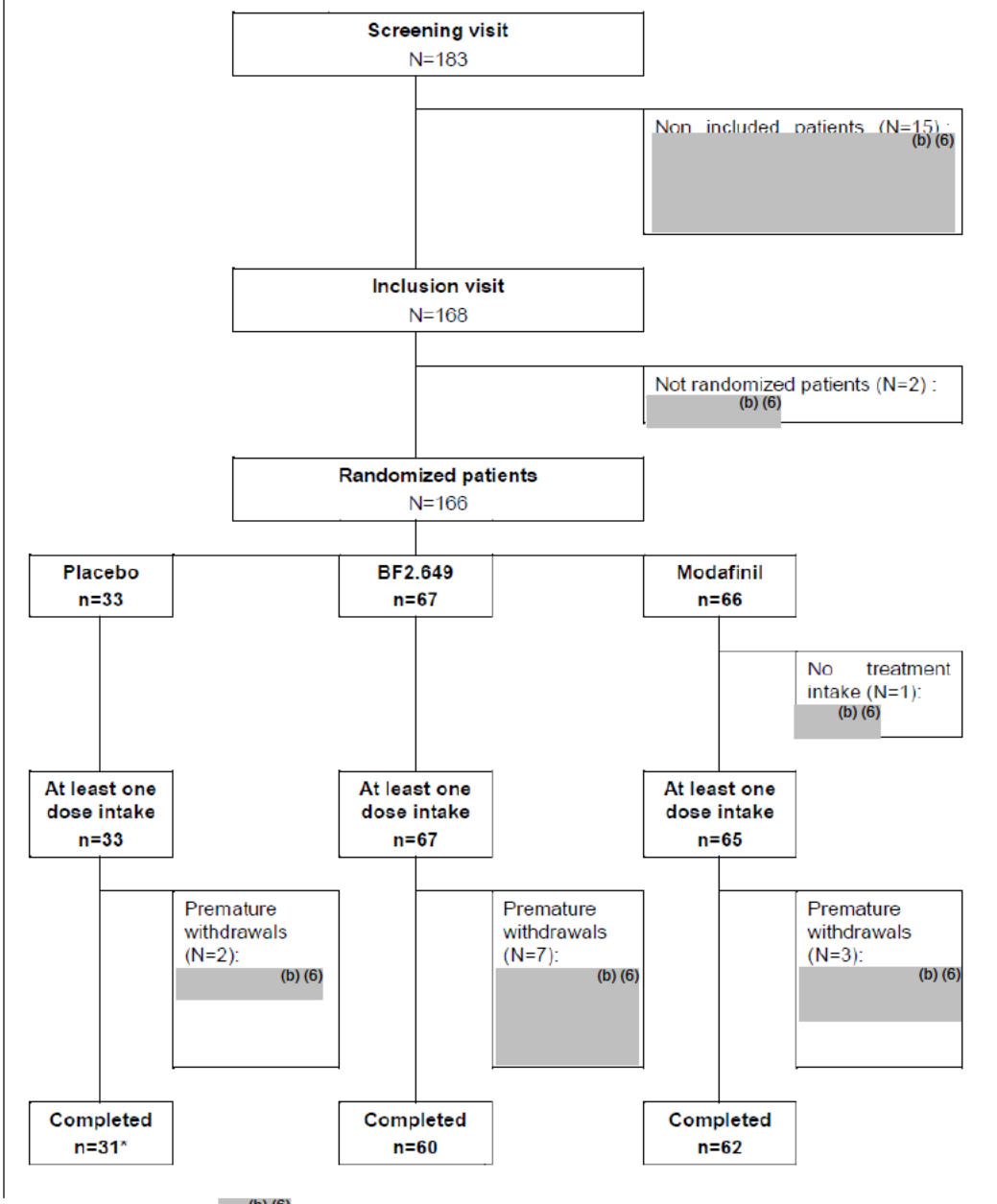
[4] Eleven patients of ITT population with premature withdrawal were excluded from the PP population: patients (b) (6) (b) (6) (major deviation), (b) (6)

[5] Premature withdrawals among patients who took at least one dose of study drug, i.e. excluding patient (b) (6) who was prematurely withdrawn without having any dose.

Source: Table 5 of Sponsor's Clinical Study Report (Page 63)

Figure 6 describes patient disposition that shows excluded patients for various reasons. The overall completion rate was 92.7% and corresponding rates for all randomized subjects are: placebo (94.0%), pitolisant (89.5%), modafinil (95.4%), and showing similarity across treatment groups. Dropouts by treatment groups were: 2 (3.1%) in placebo; 6 (9.1%) in pitolisant; 3 (4.6%) in modafinil. There were 12 (7.3%) premature withdrawals. The frequent reasons for premature withdrawal were: adverse events (50%) and/or patient decision (33.3%).

Figure 6: Patient Disposition-HARMONY 1BIS



* Including patient (b) (6) (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 (Section 11.1).
Source: Figure 3 of Sponsor's Clinical Study Report (Page 65)

Baseline demographic characteristics in all randomized population were similar. The median age of patients was between 29 to 58 years. Clear majority of participants were whites except 1 (1.4%) American Indian/Alaskan Native in pitolisant group, 1 (1.5%) African American/Black in modafinil and 1 (1.5%) Asian in modafinil.

Table 9: Summary of Demographic and Baseline Characteristics-HARMONY 1BIS (EIT Population)

Parameter	PLACEBO (N=32)	BF2.649 (N=67)	MODAFINIL (N=65)	p-value
Age [yr], median (range)	42.5 (29; 55)	37 (29; 52)	43 (32; 58)	0.405
Weight [kg], mean ± SD	80.7 ± 16.1	79.9 ± 19.5	78.5 ± 17.6	0.828
Height [cm], mean ± SD	167.6 ± 10.7	170.4 ± 9.5	168.5 ± 10.5	0.369
BMI [kg/m²], mean ± SD	28.8 ± 5.7	27.4 ± 5.6	27.6 ± 5.3	0.438
Gender [Males], % (n)	46.9 (15)	47.8 (32)	46.2 (30)	0.983
2 yrs Post-Menopause or Sterilized females, % (n)	47.1 (8/17)	31.4 (11/35)	48.6 (17/35)	0.301
Mode of Contraception				
Bill Control Pill, % (n)	44.4 (4/9)	29.2 (7/24)	27.8 (5/18)	0.792
IUD, % (n)	22.2 (2/9)	20.8 (5/24)	33.3 (6/18)	
Other Method, % (n)	33.3 (3/9)	50.0 (12/24)	38.9 (7/18)	
Ethnicity				
White, % (n)	87.5 (28)	89.6 (60)	83.1 (54)	0.722
Black or African American, % (n)	0.0 (0)	0.0 (0)	1.5 (1)	
Asian, % (n)	0.0 (0)	0.0 (0)	1.5 (1)	
American Indian or Alaska Native, % (n)	0.0 (0)	1.4 (1)	0.0 (0)	
Missing, % (n)	12.5 (4)	9.0 (6)	13.9 (9)	
History of Drug Abuse or Dependence Disorder, % (n)	0.0 (0)	1.5 (1)	0.0 (0)	0.483

Source: Table 9 of Sponsor's Clinical Study Report (Page 71)

SD=standard deviation; EIT=Extended-Intent-to-Treat: randomized pts regardless if treatment was initiated and irrespective of their outcome.

Table 10: Summary of Baseline Narcolepsy Characteristics and Efficacy Variables-HARMONY 1BIS (EIT Population)

	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: Table 10 of Sponsor's Clinical Study Report (Page 73)

3.2.4 Results and Conclusions

3.2.4.1 HARMONY 1

Primary Endpoint

The reviewer confirmed sponsor's efficacy findings (Table 10) based on imputation for the baseline or final visit scores using last observation carried forward (LOCF). The least square mean at week 8 on ESS showed a mean of 12.39 for pitolisant and 15.48 for placebo showing a statistically significantly treatment difference of -3.10 (p-value = 0.022). Patients on pitolisant group have less chance of dozing compared to patients on placebo. A total of 94 patients were included in the ITT population.

Table 11: Adjusted ESS Final Total Score at Week 8-HARMONY 1 (ITT; LME)

Visit	Placebo N=30	Pitolisant N=31
Baseline (BL)*		
N	30	31
Mean ± SD	18.9 ±2.5	17.8 ±2.5
Final (F)** at Week 8		
N	30	31
LS Mean ± SE	15.48±1.03	12.39 ±1.01
p-value		0.022
LS mean differences ± SE		-3.10 ±1.30
95% CI for differences		(-5.73, -0.46)

Source: Table 11 of Sponsor's Clinical Study Report (Page 62)
(BL)* = ESS (V2+V3)/2; Final (F)** = ESS (sum of the last two available values post-baseline)/2; CI = confidence interval; LS = least-squares; LME = linear mixed effect mode; SE = standard error; ITT = Intention to Treat; SD= Standard Deviation
Note: Increase in ESST total score indicates increased chance of dozing.

Table 11 shows the trial failed to establish non-inferiority of pitosilant relative to modafinil (p = 0.948) since 2.17 > NIM = 2.

Table 12: Adjusted ESS Final Total Score at Week 8-HARMONY 1 (ITT; LME)

Visit	Modafinil N=33	Pitolisant N=31
Baseline (BL)*		
N	33	31
Mean ± SD	18.5 ±2.7	17.8 ±2.5
Final (F)** at Week 8		
N	33	31
LS Mean ± SE	13.07 ±1.16	13.15 ±1.18
p-value		0.95
LS mean differences ± SE		0.07 ±1.11
95% CI for differences		(-2.17, 2.32)

Source: Table 13 of Sponsor's Clinical Study Report (Page 62)
(BL)* = ESS (V2+V3)/2; Final (F)** = ESS (sum of the last two available values post-baseline)/2; CI = confidence interval; LS = least-squares; LME = linear mixed effect model; SE = standard error; SD= Standard Deviation

Note: Increase in ESST total score indicates increased chance of dozing.

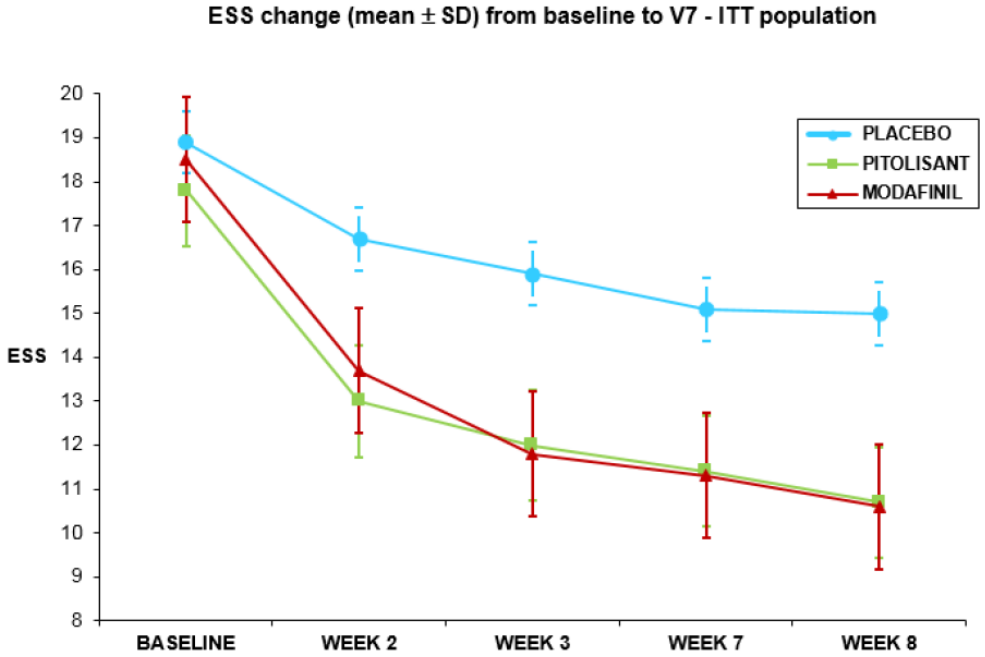
Table 13: Summary of ESS Scores [Mean +/- SD] by Visit and Treatment Group-HARMONY 1 (ITT Population)

ITT (N=94)						
	PLACEBO (N=30)		BF2.649 (N=31)		MODAFINIL (N=33)	
Visit	N	MN ± SD	n	MN ± SD	N	MN ± SD
Visit 1	30	18.1 ± 2.9	31	15.7 ± 4.4	33	17.1 ± 3.5
Visit 2	15	19.6 ± 2.7	18	17.4 ± 2.2	16	19.2 ± 2.8
Visit 3	30	19.2 ± 2.6	31	17.6 ± 2.9	33	18.4 ± 3.0
Baseline (BL)*	30	18.9 ± 2.5	31	17.8 ± 2.5	33	18.5 ± 2.7
Visit 4	30	16.7 ± 4.1	30	13.0 ± 4.8	31	13.7 ± 5.4
Visit 5	29	15.9 ± 4.1	30	12.0 ± 5.9	31	11.8 ± 6.3
Visit 6	27	15.1 ± 4.8	27	11.4 ± 5.8	29	11.3 ± 6.5
Visit 7	25	15.0 ± 4.6	26	10.7 ± 6.6	28	10.6 ± 5.6
Final (F) **	30	15.6 ± 4.7	31	11.8 ± 6.1	33	11.6 ± 6.0
Final (F) °	30	15.6 ± 4.7	31	12.0 ± 6.2	33	11.6 ± 6.0
F**-BL	30	-3.3 ± 4.1	31	-6.0 ± 6.1	33	-6.9 ± 6.1
F°-BL	30	-3.4 ± 4.2	31	-5.8 ± 6.2	33	-6.9 ± 6.2
(F**-BL)/BL (%)	30	-17.8 ± 22.4	31	-33.4 ± 32.2	33	-36.7 ± 31.4
(F°-BL)/BL (%)	30	-17.9 ± 22.4	31	-32.4 ± 33.4	33	-36.8 ± 31.6
Mean‡	30	16.0 ± 4.2	30	12.0 ± 5.5	31	12.1 ± 5.7
Mean‡‡	30	16.0 ± 4.2	31	12.3 ± 5.6	33	12.2 ± 5.5
Responders‡‡‡		% (n)		% (n)		% (n)
ESS ≤ 10	30	13.3 (4)	31	45.2 (14)	33	45.5 (15)

Source: Table 10 of Sponsor's Clinical Study Report (Page 61)

* Baseline = ESS (V2 + V3)/2.
** Final = ESS (sum of the last two available values post-baseline)/2
° Final (F) = ESS (last available value post-baseline).
‡ Mean = Arithmetic mean of all ESS values from Baseline through Final (LOCF last 2 values) visit.
‡‡ Mean = Arithmetic mean of all ESS values from Baseline through Final (LOCF last value) visit.
‡‡‡ Treatment Responders are patients with ESS Final ≤ 10

Figure 7: ESS Total Score by Visit-HARMONY 1 (ITT)



Source: Figure 4 of Sponsor's Clinical Study Report (Page 60)

The average ESS total score over time shows a general decrease in chance of sleepiness in all treatment groups. Specifically, a clear differentiation between pitolisant and placebo exists at the end of treatment as well as weeks 2, 3 and 7.

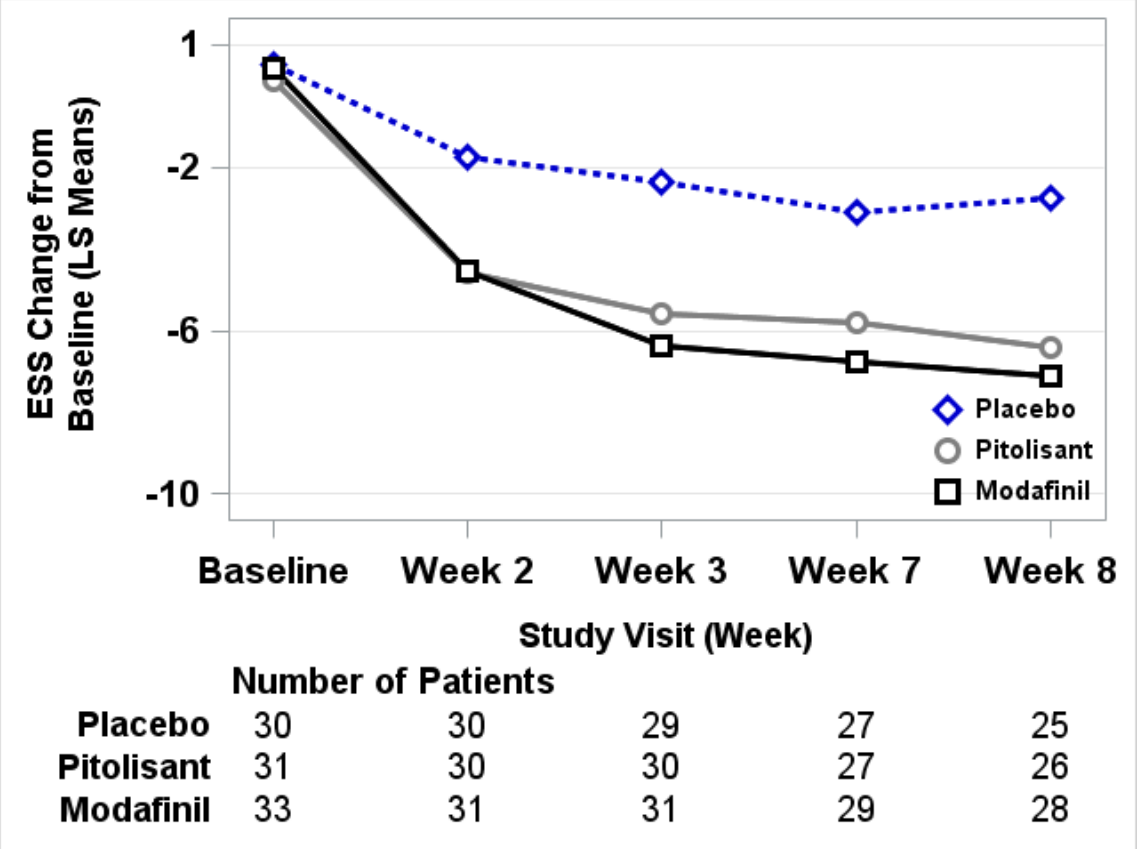
Reviewer's Additional Analysis 1: as an alternative analysis this reviewer conducted a mixed model repeated measures (MMRM; with AR (1) variance covariance structure) to confirm if Applicant's primary efficacy analysis is consistent. The model was adjusted for baseline, treatment, visit and treatment-by-visit; center as random effect; ESS values were observed at each week and not LOCF imputed.

Table 14: Adjusted Change from Baseline to Week 8 in ESS Total Score-HARMONY 1 (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)

Source: Reviewer

Figure 8: Change in ESS Total Score by Visit-HARMONY 1 (ITT)



Number of Patients					
Placebo	30	30	29	27	25
Pitolisant	31	30	30	27	26
Modafinil	33	31	31	29	28

Source: Reviewer

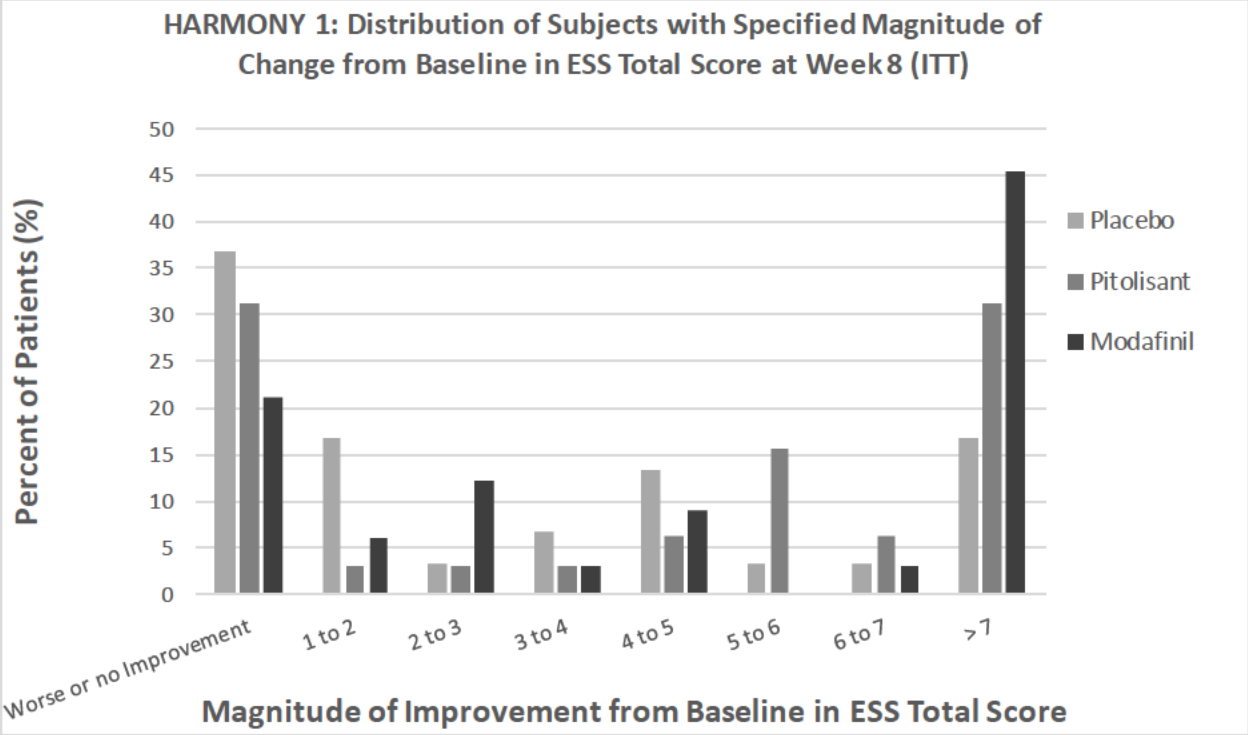
Additional analysis was conducted using endpoint: change from baseline to *average of the last two visits*. Estimated treatment effect for pitolisant-placebo (-3.11 (1.05); 95% CI: [-5.19, -1.04]; p = 0.003) and pitolisant-modafinil (0.72 (1.05); 95% CI: [-1.35, 2.79]; p = 0.49) yielded similar conclusions to applicant's analysis based on ANCOVA.

Sponsor's analyses based on the per-protocol dataset were similar to the primary efficacy analyses. Supportive analyses yielded similar results: using ANCOVA (without center effect), with or without adjustment for ESS baseline score.

Reviewer's Note: This reviewer has included a figure to visualize the distribution of change in ESS total score (Figure 9) for HARMONY 1. Distribution of improved subjects is categorized in a 2-unit bin; subjects who didn't show improvement are located in the left corner bins.

Figure 9 shows distribution of change from baseline in ESS total score at week 8. A large proportion of subjects in the placebo group had a '1-2' magnitudes of improvement; considerable proportion of subjects in the pitolisant showed improvement of '5-6' magnitude. Caution should be exercised when interpreting the distributional plot presented here. The trial is considered small in sample size and only very few subjects contribute data in each bin.

Figure 9: Percent of Patients with Specified Magnitude of ESS Total Score Improvement at Week 8 (ITT; HARMONY 1)



Source: Reviewer's Result

Secondary Endpoints
MWT and SART

Table 15: Summary of Efficacy Analysis Results for MWT and SART-HARMONY 1 (ITT)

	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

Source: Table 16 of Sponsor's Clinical Study Report (Page 64) (Ref: Tables 14.2.3.1.13; 14.2.3.1.14; 14.2.3.1.17; 14.2.3.1.19; 14.2.3.1.21)
The geometric means between treatment groups (ratio of mean of Pitolisant/Placebo) were compared

based on t-test (pooled).

The rate of geometric mean in MWT (wakefulness) improved in the pitolisant group compared with placebo (p = 0.044). Also, pitolisant improved the rate of geometric mean in SART-NOGO error scores (p=0.042).

Reviewer's Comment 1: In their clarification note to the FDA on 27 March 2019, a response to FDA information request on 27 March 2019, the Applicant conducted additional analyses on secondary endpoints (MWT and/or SART) using non-parametric method Mann-Whitney test, with and without imputation of last observed value.

(a) The Mann-Whitney test on MWT in HARMONY 1 (P07-03) was consistent with the specified Student's t-test.
(b) The Mann-Whitney and Student's t-test results on MWT in HARMONY 1BIS (P09-15) were not statistically significant and not consistent with the results of the specified linear fixed effect model.
(c) The Mann-Whitney test on MWT in HARMONY CTP (P11-05) was consistent with the specified Student's t-test.

ESS Responder Rate: ESS ≤ 10

Responders were classified based on cutoff, ESSF≤10. Calculated responder rates by treatment groups were: 13.3% in the placebo group, 45.2% in the pitolisant group and 45.5% in the modafinil group (Table 15). The odds of response in the pitolisant group were significantly greater than placebo [OR=7.86; 95% CI: (1.59, 38.86); p = 0.013].

Table 16: Summary of Analysis of Responder Rate-HARMONY 1 [OR Pitolisant vs. Placebo and Pitolisant vs. Modafinil] - Logistic Regression Model (ITT)

Odds Ratio	ITT (N=94)					
	Comparison	**Control**	**BF**	**Est.**	**95% CI**	**p**
ESS ≤ 10	Pit/PB	13.3 (4)	45.2 (14)	7.86	[1.59; 38.86]	0.013
	Pit/MD	45.5 (15)	45.2 (14)	1.09	[0.31; 3.81]	0.892

Source: Table 14 of Sponsor's Clinical Study Report (Page 63)
OR = Odds Ratio of treatment responders adjusted on ESS Baseline (Logistic Regression Model)

Daily Rate of Cataplexy (DRC)

As a supportive analysis, daily cataplexy rates were computed for exposed population (patients with at least one occurrence of cataplexy crisis at baseline or during treatment).

Table 17: Analysis results for daily rates of complete and partial cataplexy episodes (DRC) - Exposed Population (HARMONY 1)

	Placebo	BF2.649	Modafinil
Number of exposed patients	14	20	23
Baseline DCR* [Geometric mean]	0.4	0.5	0.4
Final DCR* [Geometric mean]	0.4	0.2	0.3
Comparison BF2.649 versus placebo			
RR		0.38	
95%CI		[0.15; 0.93]	
p-value		0.034	
Comparison modafinil versus placebo			
RR		0.70	
95%CI		[0.297; 1.629]	
p-value		0.396	
Comparison BF2.649 versus modafinil			
RR			0.54
95%CI			[0.24; 1.23]
p-value			0.138

Source: Table 22 of Sponsor's Clinical Study Report (Page 70)

DCR = Daily Cataplexy Rates, *For patients with no cataplexy at baseline or during treatment period, imputation value was determined by 0.5/number of days.

Exposed Population = the subgroup of patients who had at least one occurrence of a given event (cataplexy) at baseline or during treatment.

Reviewer's Comment 2 (Daily Rate of Cataplexy): A subgroup analysis was conducted on select number of patients who were identified to have cataplectic in HARMONY 1. Missing or zero cataplectic events were imputed by value 0.5 in the analysis. The choice, 0.5 (the average of no crises 0 and smallest possible count 1), for the missing or zero cataplectic events is to allow calculation on a logarithmic scale when computing the geometric means. Pitolisant demonstrated reduction over placebo on the secondary endpoint of mean daily rate of cataplexy [rate ratio=0.38, 95% CI (0.15; 0.93); p=0.034] *when subjects with zero or missing cataplectic events were imputed*. In response to FDA information request (15 March 2019), the Applicant clarified the rationale for imputation and presented analysis results when *subjects with zero or missing cataplectic events were ignored*, in which pitolisant does not demonstrate improvement over placebo [rate ratio = 0.45; 95% CI (0.14, 1.48); p=0.17]. Placebo and pitolisant groups had 10 and 15 subjects who had non-zero or no missing observed cataplectic events, respectively. To assess sensitivity of Applicant's choice of 0.5 as a replacement value, other values were also considered: 0.1, 0.25, 0.75 where the p values were nominally significant.

Applicant's findings could generally be considered as supportive exploratory analysis since this was not a pre-specified analysis with prospective plan to control type 1 error rate. In addition, post-hoc analysis based on outcome-defined subgroups (exposed-population based on cataplexy events) violates the randomization principle by creating imbalance of known and unknown confounds among the treatment groups. This leads to invalid statistical comparisons.

Reviewer's Additional Analysis 2: 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 18: 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: Reviewer
*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 ($p = 0.906$).

3.2.4.2 HARMONY CTP

Primary Endpoint

The primary efficacy for anticataplectic activity was assessed by the change in the average number of cataplexy attacks per week (weekly rate of cataplexy) between the 2 weeks of baseline (Day-14 to Day 0) and 4 weeks of stable treatment period (Day21 to Day49). Patients reported both partial and complete cataplexy attacks between visits 1 to 6. A total of 105 patients were included in the ITT population. The reviewer confirmed sponsor's efficacy findings (see Table 18).

Summary statistics such as the geometric means, arithmetic means and median of the weekly rate of cataplexies (WRC) are displayed for each week in Table 18 for ITT population. Those who took pitolisant have significantly reduced risk of cataplectic events compared to those in the placebo group [rate ratio: 0.51, 95% CI: (0.43, 0.6); $p < 0.0001$]. Ratio of rates was used to summarize the effect of pitolisant relative to placebo.

Table 19: Summary of Weekly Rate of Cataplexy Episodes (WRC)-HARMONY CTP [Geometric Mean, Arithmetic Mean (SEM)] – ITT Population

	Placebo (N=51)					BF2.649 (N=54)					Total (N=105)				
Visit - Week	N	GMT [95% IC] (1)	GMT ♦ [95% IC] (2)	Arith Mean ♦ (SEM)	Median (Q1-Q3)	n	GMT [95% IC] (1)	GMT ♦ [95% IC] (2)	Arith Mean (SEM) ♦	Median (Q1-Q3)	n	GMT [95% IC] (1)	GMT ♦ [95% IC] (2)	Arith Mean ♦ (SEM)	Median (Q1-Q3)
V2 - Week 1	51	6.77 [5.46;8.39]	6.77 [5.46;8.39]	9.22 (1.24)	6.00 [4.00 ; 13.00]	54	8.62 [7.15;10.39]	8.62 [7.15;10.39]	10.96 (1.21)	9.00 [5.00 ; 14.00]	105	7.66 [6.65;8.83]	7.66 [6.65;8.83]	10.11 (0.86)	7.00 [4.00 ; 13.00]
V2 - Week 2	51	7.57 [6.24;9.19]	7.57 [6.24;9.19]	10.04 (1.48)	6.00 [5.00 ; 13.00]	54	9.28 [7.55;11.40]	9.28 [7.55;11.40]	12.39 (1.59)	8.00 [5.00 ; 16.00]	105	8.41 [7.30;9.68]	8.41 [7.30;9.68]	11.25 (1.09)	8.00 [5.00 ; 15.00]
Baseline (BL) - (Wk1+Wk2)/2	**51**	**7.31 [6.02;8.87]**	**7.31 [6.02;8.87]**	**9.63 (1.33)**	**6.50 [4.50 ; 12.00]**	**54**	**9.15 [7.60;11.01]**	**9.15 [7.60;11.01]**	**11.68 (1.36)**	**8.50 [5.50 ; 15.50]**	**105**	**8.20 [7.18;9.37]**	**8.20 [7.18;9.37]**	**10.68 (0.95)**	**7.00 [5.00 ; 14.00]**
V3 - Week 3	51	4.87 [3.11;7.62]	4.87 [3.11;7.62]	10.37 (1.63)	6.00 [3.00 ; 16.00]	54	4.39 [2.92;6.59]	4.39 [2.92;6.59]	9.80 (2.50)	6.00 [3.00 ; 12.00]	105	4.61 [3.43;6.21]	4.61 [3.43;6.21]	10.08 (1.50)	6.00 [3.00 ; 13.00]
V3 - Week 4	51	4.24 [2.59;6.95]	4.24 [2.59;6.95]	10.76 (2.44)	6.00 [3.00 ; 14.00]	54	3.29 [2.07;5.23]	3.29 [2.07;5.23]	7.56 (1.10)	6.00 [2.00 ; 10.00]	105	3.72 [2.66;5.19]	3.72 [2.66;5.19]	9.11 (1.32)	6.00 [2.00 ; 13.00]
V4 - Week 5	51	5.13 [3.29;7.98]	4.98 [3.22;7.71]	10.84 (1.98)	7.00 [3.00 ; 16.00]	54	3.49 [2.31;5.27]	3.49 [2.31;5.27]	7.15 (1.11)	4.00 [2.00 ; 9.00]	105	4.21 [3.12;5.67]	4.15 [3.08;5.58]	8.94 (1.13)	6.00 [3.00 ; 13.00]
V5 - Week 6	51	3.86 [2.28;6.53]	3.73 [2.22;6.27]	10.11 (1.95)	6.00 [3.00 ; 16.00]	54	2.03 [1.27;3.27]	2.07 [1.28;3.33]	5.27 (0.88)	3.00 [1.00 ; 7.00]	105	2.78 [1.95;3.95]	2.75 [1.94;3.91]	7.62 (1.07)	5.00 [2.00 ; 9.00]
V5 - Week 7	51	4.43 [2.79;7.05]	4.29 [2.71;6.77]	10.01 (1.96)	6.00 [3.00 ; 14.00]	54	1.97 [1.23;3.17]	2.00 [1.24;3.23]	4.86 (0.78)	3.00 [2.00 ; 5.00]	105	2.92 [2.09;4.09]	2.90 [2.08;4.05]	7.36 (1.06)	4.00 [2.00 ; 9.00]
V5 - Week 8	51	4.00 [2.46;6.50]	3.87 [2.40;6.25]	9.74 (1.95)	6.00 [3.00 ; 15.00]	54	1.77 [1.09;2.87]	1.80 [1.11;2.92]	4.77 (0.77)	3.00 [1.00 ; 6.00]	105	2.63 [1.86;3.72]	2.61 [1.85;3.68]	7.18 (1.05)	4.00 [1.00 ; 10.00]
V6 - Week 9	51	3.52 [2.10;5.92]	3.41 [2.04;5.69]	9.46 (1.96)	6.00 [3.00 ; 15.00]	54	1.72 [1.08;2.75]	1.75 [1.09;2.80]	4.31 (0.68)	3.00 [1.00 ; 5.00]	105	2.44 [1.72;3.46]	2.42 [1.71;3.42]	6.81 (1.04)	4.00 [1.00 ; 7.00]
V7 - Week 10	51	3.62 [2.24;5.85]	3.50 [2.18;5.61]	9.15 (1.97)	5.00 [2.00 ; 15.00]	54	1.52 [0.90;2.57]	1.54 [0.91;2.62]	5.78 (1.65)	2.00 [0.00 ; 7.00]	105	2.32 [1.61;3.32]	2.30 [1.60;3.29]	7.41 (1.28)	4.00 [1.00 ; 8.00]
Stable Dose (S) - (Wk6+Wk7+Wk8+Wk9)/4	**51**	**4.51 [2.90;7.02]**	**4.36 [2.82;6.74]**	**9.83 (1.94)**	**6.00 [3.00 ; 15.00]**	**54**	**2.27 [1.51;3.41]**	**2.31 [1.53;3.48]**	**4.80 (0.74)**	**3.00 [1.25 ; 6.00]**	**105**	**3.17 [2.34;4.29]**	**3.14 [2.33;4.24]**	**7.24 (1.04)**	**4.50 [1.75 ; 9.00]**
S/BL	**51**	**0.62 [0.43;0.90]**	**0.60 [0.41;0.86]**	**1.02 (0.11)**	**0.93 [0.57 ; 1.23]**	**54**	**0.25 [0.17;0.36]**	**0.25 [0.18;0.36]**	**0.50 (0.05)**	**0.40 [0.25 ; 0.76]**	**105**	**0.39 [0.30;0.51]**	**0.38 [0.29;0.50]**	**0.75 (0.07)**	**0.65 [0.29 ; 0.97]**
V7/BL	51	0.50 [0.33;0.75]	0.48 [0.32;0.72]	0.94 (0.12)	0.78 [0.53 ; 1.13]	54	0.17 [0.10;0.27]	0.17 [0.10;0.28]	0.56 (0.09)	0.35 [0.18 ; 0.71]	105	0.28 [0.20;0.40]	0.28 [0.20;0.39]	0.75 (0.08)	0.57 [0.23 ; 1.00]

Source: Table 11.4-1 of Sponsor's Clinical Study Report (Page 86) (Ref. Table 14.2.1.1.1)

(1) For patients terminating the trial before completion, the final value were calculated as the mean of the two last known periods (LOCF method).

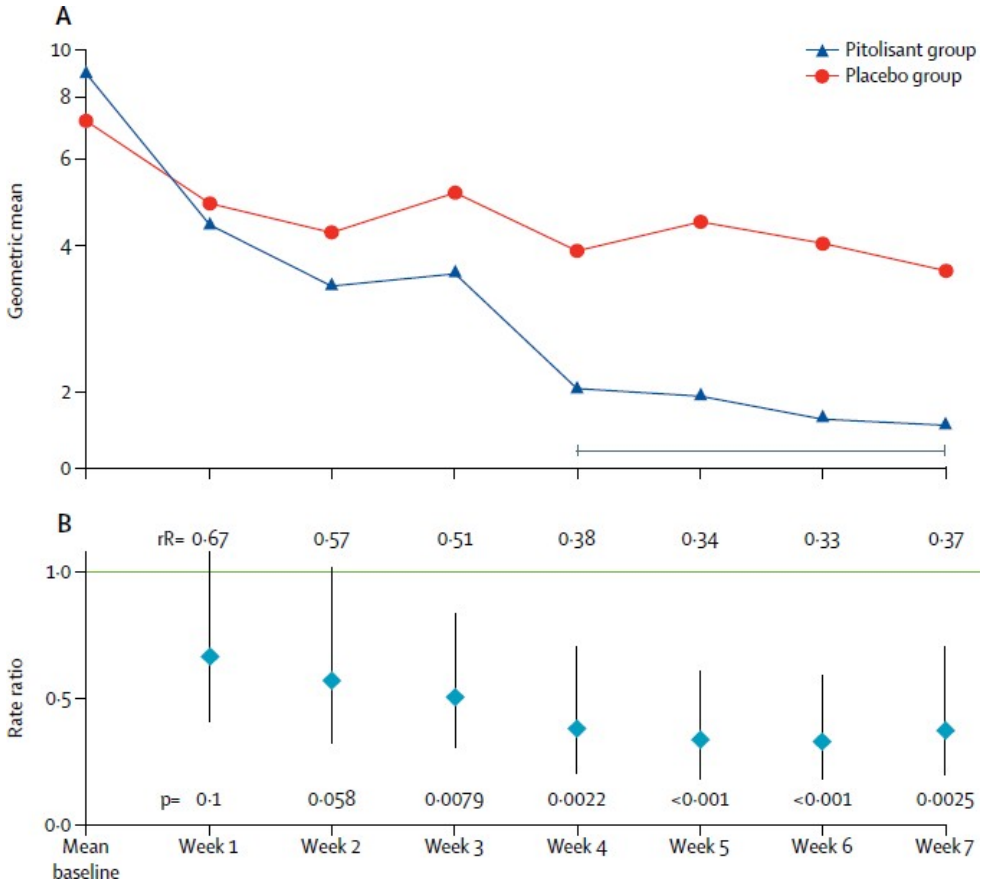
(2) For patients without post-baseline values, the final value was assimilated with baseline (BOCF method).

For estimating ratios (arithmetic means), a value of 1 was added to numerator and denominator to avoid 0 values (i.e. (S+1)/(BL+1) and (V7+1)/(BL+1)).

For geometric means, in case of WRC=0 at a given week, a value of 0.1 was imputed. For arithmetic means, observed values were used with LOCF method for imputation of missing data

♦Change from CSR Version 1.0 to 2.0

Figure 10: Geometric Mean of the Number of Cataplexies at Every Week from Baseline to W9 (Week 7 treatment) -HARMONY CTP



Source: Figure 11.4:1 of Sponsor's Clinical Study Report (Page 87)
(A) Geometric mean of weekly cataplexy rates.
(B) Rate ratio (rR) of pitolisant or placebo adjusted for baseline (means of weeks 1 and 2) with 95% CI and p values for each week (no missing values imputed) [Source: Szakacs, 2017]

Results showed a decrease in WRC from baseline of 38% and 75% for placebo and pitolisant respectively. The treatment effect of pitolisant versus placebo on WRC was evaluated by using a mixed non-linear model characterized by *Poisson Regression* during the 4-week stable treatment phase (D21 to D49) adjusted for baseline (D-14 to D0). Center was considered as a random effect to account for center heterogeneity. The Poisson Regression analysis used LOCF method with the average of the last 2 available values [Table 19]. Two additional models, *Quasi Poisson Regression model* and a *negative binomial regression model*, were also considered to account for potential over-dispersion. Resulting treatment effect and corresponding statistics were comparable to the main analysis model.

The weekly rate of cataplexies observed in pitolisant group was nearly half of the placebo group with rate ratio, rR = 0.51. The difference between the treatment groups was statistically significant in which the WCR decreased from 7.31 to 4.36 for placebo and 9.15 to 2.31 for pitolisant (95% CI [0.43, 0.60]; p<0.0001).

Table 20: Analysis on Weekly Rate of cataplexy (Last Four Weeks, WRC ≥0) – Non-Linear Mixed Effects (ITT)-HARMONY CTP

						Ratio of geometric mean		
ITT- LOCF method with the average of the last 2 available values								
Analysis	Estimate	SE*	95% LCL	95% UCL	p-value	Exp† Estimate	Exp* LCL	Exp* UCL
Poisson	-0.67	0.082	-0.83	-0 50	<.0001	**0.51**	**0.43**	**0.60**
Quasi Poisson♦	-0.73	0.16	-1.06	-0.41	<.0001	0.4804	0 35	0.66
Negative Binomial	-0.70	0.18	-1.06	-0 34	0.0002	0.49	0 34	0.71

Source: Table 11.4-2 of Sponsor's Clinical Study Report (Page 89)
*Standard Error; †Exponentiated
♦ Change fromCSR Version 1.0 to 2.0

Table 21: Analysis Results of WRC by Stable Dose (Last Four Weeks; WRC ≥0): Non-Linear Mixed Effects Models (ITT)-HARMONY CTP

ITT-LOCF - Poisson Regression ♦									
	N in each arm	Estimate	SE	Pr > |t|	95% LCL	95% UCL	Exp Estimate	Exp LCL	Exp UCL
20mg - pl	Pitolisant 20mg: 9 / Placebo: 48	-0.94	0.19	<.0001	-1.31	-0.56	0.39	0.275	0.57
40mg - pl	Pitolisant 40mg: 35 / Placebo: 48	-0.47	0.10	<.0001	-0.67	-0.27	0.62	0.51	0.76
40mg - 20mg	Pitolisant 40mg: 35 / Pitolisant 20mg: 9	0.46	0.20	0.024	0.063	0.86	1.59	1.06	2.36
ITT- LOCF - Quasi Poisson ♦									
20mg - pl	Pitolisant 20mg: 9 / Placebo: 48	-0.95	0.37	0.013	-1.69	-0.21	0.39	0.18	0.81
40mg - pl	Pitolisant 40mg: 35 / Placebo: 48	-0.57	0.19	0.0054	-0.96	-0.17	0.57	0.387	0.84
40mg - 20mg	Pitolisant 40mg: 35 / Pitolisant 20mg: 9	0.38	0.39	0.340	-0.40	1.16	1.46	0.67	3.18
ITT - LOCF- Negative binomial									
20mg - pl	Pitolisant 20mg: 9 / Placebo: 48	-0.94	0.36	0.01	-1.67	-0.22	0.39	0.19	0.80
40mg - pl	Pitolisant 40mg: 35 / Placebo: 48	-0.62	0.21	0.004	-1.04	-0.20	0.54	0.35	0.82
40mg - 20mg	Pitolisant 40mg: 35 / Pitolisant 20mg: 9	0.32	0.38	0.39	-0.42	1.07	1.38	0.65	2.92

Source: Table 11.4-4 of Sponsor's Clinical Study Report (Page 90)
♦ Change fromCSR Version 1.0 to 2.0

The higher stable dose of pitolisant (40mg) is statistically significant compared to placebo across the three methods.

Reviewer's Comment: For the primary efficacy model in HARMONY CTP, the missing values were LOCF imputed (average of the last two available values). Thus, patients who discontinued or terminated the trial before completion were assumed observed (5 in pitolisant, 9 in placebo). In response to our information request (March 15, 2019) the applicant revealed both negative binomial and Poisson regression results without imputation were consistent with the primary analysis result. The results were confirmed by the reviewer.

Secondary Endpoints

Weekly Rate of Cataplexy (WRC) episodes during the last two weeks of treatment

Table 22: Summary of Change in Weekly Rate of Cataplexy Episodes in Last Two Weeks of Treatment (WRC) [Geometric Mean, Arithmetic Mean (SEM), Median (Q1; Q3)] – ITT Population (HARMONY CTP)

	Placebo (N=51)					Pitolisant (N=54)					Total (N=105)				
Visit - Week	n	GMT [95% IC] (1)	GMT [95% IC] (2) ♦	Arith Mean (SEM) ♦	Median (Q1-Q3)	n	GMT [95% IC] (1)	GMT [95% IC] (2) ♦	Arith Mean (SEM) ♦	Median (Q1-Q3)	n	GMT [95% IC] (1)	GMT [95% IC] (2) ♦	Arith Mean (SEM) ♦	Median (Q1-Q3)
Baseline (BL) - (Wk1+W 2)/2	51	7 31 [6 02;8 87]	7 31 [6 02;8 87]	9 63 (1 33)	6 50 [4 50 ; 12 00]	54	9 15 [7 60;11 01]	9 15 [7 60;11 0 1]	11 68 (1 36)	8 50 [5 50 ; 15 50]	105	8 20 [7 18;9 37]	8 20 [7 18;9 37]	10 68 (0 95)	7 00 [5 00 ; 14 00]
Final (F) - (Wk8+Wk9)/2	51	4 26 [2 72;6 66]	4 12 [2 65;6 39]	9 60 (1 94)	5 50 [3 00 ; 15 00]	54	1 99 [1 29;3 05]	2 02 [1 31;3 11]	4 54 (0 71)	3 00 [1 00 ; 6 00]	105	2 88 [2 10;3 94]	2 86 [2 09;3 90]	7 00 (1 04)	4 00 [1 50 ; 8 50]
F/BL	51	0 58 [0 40;0 85]	0 56 [0 39;0 82]	0 99 (0 11)	0 92 [0 53 ; 1 25]	54	0 22 [0 15;0 32]	0 22 [0 15;0 32]	0 49 (0 06)	0 38 [0 21 ; 0 67]	105	0 35 [0 26;0 46]	0 35 [0 26;0 46]	0 73 (0 06)	0 58 [0 27 ; 1 00]

(1) For patients terminating the trial before completion, the final value were calculated as the mean of the two last known periods (LOCF method).
(2) For patients without post-baseline values, the final value were assimilated with baseline (BOCF method).
For estimating ratios (arithmetic means), a value of 1 was added to numerator and denominator to avoid 0 values (i.e. (S+1)/(BL+1) and (V7+1)/(BL+1)). For geometric means, in case of WRC=0 at a given week, a value of 0.1 was imputed.
For arithmetic means, observed values were used with LOCF method for imputation of missing data
♦ Change from CSR Version 1.0 to 2.0

Source: Table 11.4-5 of Sponsor's Clinical Study Report (Page 91)

Table 23: Analysis on Weekly Rate of Cataplexy (Last Two Weeks; WRC ≥0) – Non-Linear Mixed Effects Models (ITT)-HARMONY CTP

						Ratio of geometric mean		
Analysis	Estimate	Standard Error	95% Confidence Limits	95% Confidence Limits	P-value	Exponentiated Estimate	Exponentiated Lower Confidence Limit	Exponentiated Upper Confidence Limit
IT – LOCF method with the average of the last 2 available values								
Poisson	-0.69	0.084	-0.86	-0.53	<.0001	**0.50**	**0.42**	**0.60**
Quasi Poisson ♦	-0.76	0.17	-1.10	-0.42	<.0001	0.47	0.33	0.66
Negative Binomial	-0.70	0.19	-1.08	-0.32	0.0004	0.50	0.34	0.73
IT – BOCF method								
Poisson	-0.58	0.084	-0.75	-0.41	<.0001	0.56	0.47	0.66
Quasi Poisson ♦	-0.66	0.17	-0.99	-0.32	0.0002	0.52	0.37	0.73
Negative Binomial	-0.63	0.19	-1.01	-0.24	0.0015	0.53	0.36	0.78

Source: Table 11.4-7 of Sponsor's Clinical Study Report (Page 93)

On the secondary endpoint (WRC in the last two weeks of treatment), pitolisant showed superiority to the placebo group (95% CI: [0.42, 0.59], $p < 0.0001$), where the geometric mean WRC in the pitolisant group is half of the placebo group (rR=0.50).

MWT

Table 24: Summary of Efficacy Analysis Results for MWT (Geometric mean, Arithmetic mean) (ITT)-HARMONY CTP

		ITT			
group	**Week**	**n**	**Geom Mean**	**Arith Mean (SEM)**	**Median (Q1-Q3)**
PLACEBO	Baseline (BL)	51	4.3 [3.0;6.2]	7.8 (1.1)	4.5 [2.3 ; 11.5]
	Final (F)	51	4.6 [3.1;6.8]	9.8 (1.6)	5.3 [2.0 ; 13.1]
	F/BL	51	1.1 [0.8;1.4]	1.7 (0.3)	1.0 [0.5 ; 2.1]
PITOLISANT	Baseline (BL)	54	3.7 [2.7;5.2]	6.9 (1.0)	4.0 [1.7 ; 7.2]
	Final (F)	54	7.1 [4.9;10.3]	14.1 (1.9)	9.1 [2.1 ; 23.8]
	F/BL	54	1.9 [1.4;2.5]	3.0 (0.4)	1.7 [1.1 ; 3.7]
Total	Baseline (BL)	105	4.0 [3.2;5.1]	7.3 (0.8)	4.4 [2.0 ; 9.5]
	Final (F)	105	5.7 [4.4;7.5]	12.0 (1.2)	6.8 [2.1 ; 17.6]
	F/BL	105	1.4 [1.2;1.7]	2.4 (0.3)	1.2 [0.7 ; 3.0]

Source: Table 11.4-17 of Sponsor's Clinical Study Report (Page 103) (Ref: Tables 14.2.10.1.1; 14.2.10.1.2)

**Missing values were estimated using the linear relationship between MWT and ESS*

The geometric means between treatment groups (ratio of mean of Pitolisant/Placebo) were compared based on t-test (pooled).

The geometric mean in MWT (wakefulness) improved in the pitolisant group compared with placebo (rR=1.78, 95% CI: [1.22, 2.60], p = 0.003) where the MWT rate in pitolisant is 78% higher than placebo. Also, pitolisant improved the rate of geometric mean in SART-NOGO error scores (p=0.042).

ESS Score

The mean ESS score improved significantly in pitolisant group compared to placebo where the treatment effect was -3.42 (95%CI [-5.03, -1.92]; p<0.0001; ANCOVA LOCF). The result was also similar for only observed cases.

ESS Responder Rate: **ESS ≤ 10**

The proportion of pitolisant responders (39.2%) was statistically significantly different from placebo (18.0%) where calculated odds ratio (OR) is 3.28 (95% CI [1.08, 9.92]; p=0.035) (Table 24).

Table 25: Summary of Treatment Responder based on ESS (Type 1) [% (n/N)] (ITT)-HARMONY CTP

	ITT		PP	
	PLACEBO (N=51)	**BF2.649 (N=54)**	**PLACEBO (N=42)**	**BF2.649 (N=49)**
Responder	**% (n/N)**	**% (n/N)**	**% (n/N)**	**% (n/N)**
Type 1 = ESSF ≤ 10 OR=3.28 95%CI: (1.08, 9.92) p=0.035	18.0 (9/50)	39.2 (20/51)	21.4 (9/42)	38.8 (19/49)

Source: Table 11-4-13 of Sponsor's Clinical Study Report (Page 99)
Type 1: definition based on final ESS score ≤ 10; OR = odds ratio (Ref. Table 14.2.6.2.1).

Also, the risk ratio demonstrated a significant treatment effect (rR=2.11 (95%CI [1.04; 4.29], p=0.039).

Based on type 2 definition ($ESS_F \leq 10$ or $ESS_F - ESS_{BL} \geq 3$), the odds of response in the pitolisant group were significantly greater than that in the placebo group (OR=4.26 (95% CI [1.72, 10.5]; p=0.002), where the proportion of responders in pitolisant and placebo were 68.6% and 34.0%, respectively.

Reviewer's Additional Analysis (Van Elteren Method and Funnel Plot)

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 11 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 the table below.

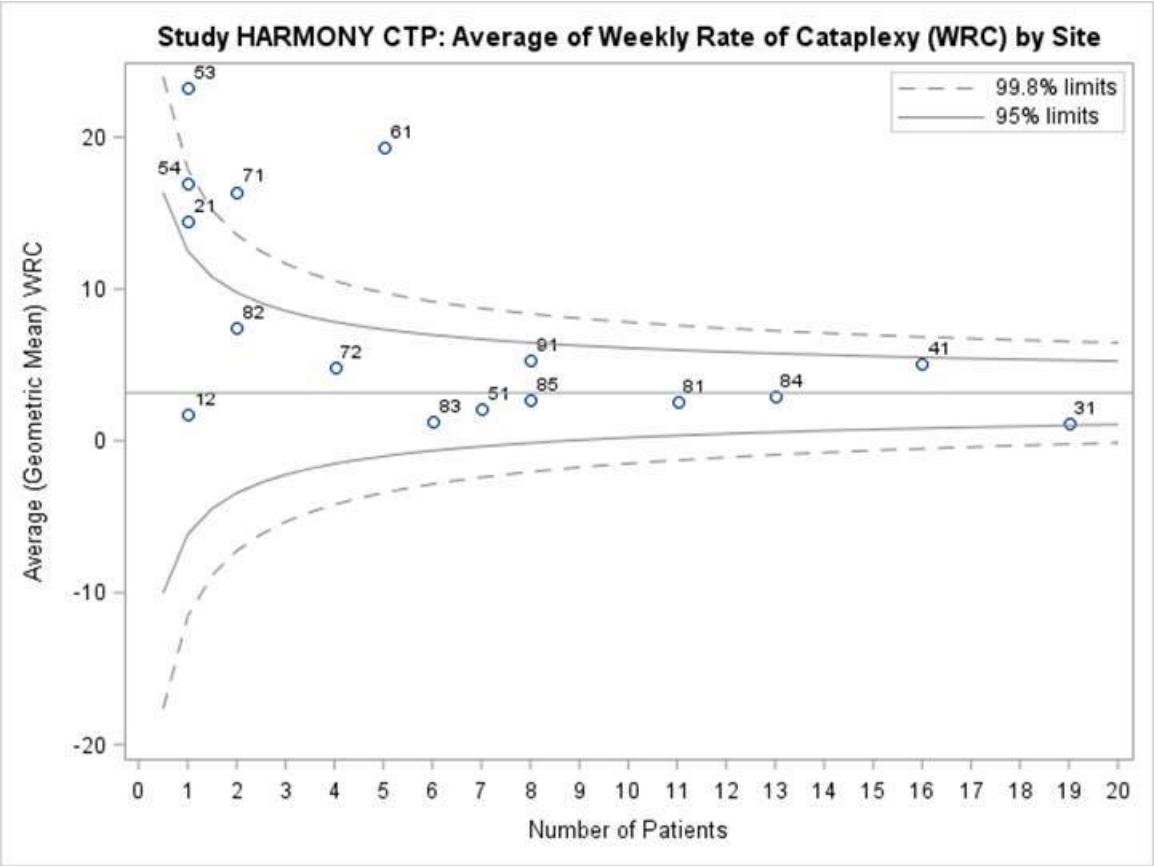
Table 26: Sample Size by Study Site-HARMONY CTP

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: Reviewer

Figure 11: 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: Reviewer

3.2.4.3 HARMONY 1BIS

Primary Endpoint

Pitolisant was statistically significantly superior to placebo in the mean change in ESS total score at week 8, with a least square mean treatment difference from placebo of -2.19 (p-value = 0.03).

Patients treated with pitolisant have decreased chance of falling asleep compared to patients in the placebo group. The reviewer confirmed sponsor's efficacy findings (Table 26).

The primary analysis was based on covariance ANCOVA where the model for the final ESS was adjusted for baseline ESS, fixed factor treatment and random effect center. The conclusion was similar across the per-protocol† population.

†Per-Protocol Population: all patients in the ITT population who completed the study until at least V6 (i.e., having one value at V6 or V7), and without any major protocol deviation related to primary endpoint.

Table 27: Summary of ESS Scores [Mean +/- SD] by Visit and Treatment Group (ITT Population)-HARMONY 1BIS

	ITT (N=163)					
	PLACEBO (N=32)		PITOLISANT (N=66)		MODAFINIL (N=65)	
Visit	n	MN ± SD	n	MN ± SD	n	MN ± SD
Visit 1	26	16.4 ± 4.8	48	16.6 ±3.8	48	16.1 ± 5.6
Visit 2	20	18.1 ± 2.4	58	18.1 ±2.4	54	18.0 ± 3.1
Visit 3	31	18.1 ± 2.6	66	18.5 ±2.7	64	18.2 ± 3.0
Visit 4	31	15.3 ± 4.4	65	14.7 ±5.1	64	12.7 ± 5.4
Visit 5	31	14.4 ± 5.3	63	13.9 ±5.5	64	10.9 ± 6.2
Visit 6	30	14.3 ± 6.1	60	13.3 ±5.6	62	10.5 ± 6.2
Visit 7	29	14.3 ± 6.1	61	13.6 ±5.5	62	10.4 ± 6.2
Visit 8	29	14.7 ± 6.2	60	14.1 ±5.7	59	11.7 ± 5.9
Baseline (BL)*	32	18.2 ± 2.3	66	18.3 ±2.4	65	18.1 ± 2.8
Final (F)**	31	14.5 ± 5.9	66	13.7 ±5.4	64	10.4 ± 6.0
Final (F) °	32	14.6 ± 5.8	66	13.7 ±5.4	65	10.3 ± 6.1
F°-BL	32	-3.6 ± 5.6	66	-4.6 ± 4.6	65	-7.8 ± 5.9
F**-BL	31	-3.6 ± 5.6	66	-4.6 ± 4.6	64	-7.8 ± 5.8
(F°-BL)/BL	32	-20.0%	66	-25.8%	65	-43.3%
(F**-BL)/BL	31	-20.3%	66	-25.7%	64	-43.3%
Mean‡	32	14.8 ± 5.1	66	14.0 ±5.0	65	11.2 ± 5.4

Source: Table 15 of Sponsor's Clinical Study Report (Page 78)
NOTE: Patients (b) (6) (placebo) and (b) (6) (modafinil) had missing data for all visits (questionnaires); ESSBL and ESSF composite scores were provided by the investigator in the CRFs.
* ESSBL = (ESSV2 + ESSV3)/2; or (ESSV1 + ESSV3)/2 if ESSV2 is missing; or (ESSV1 + ESSV2)/2 if ESSV3 is missing; ** Final (F)= ESS (sum of the last 2 available values post baseline)/2;
°Final (F)= ESS (last available value post baseline); or Last Observation Carried Forward (LOCF) if ESSV7 is missing; ‡ MEAN = Arithmetic mean across all visits between ESSBL and ESSF.

Table 28: Adjusted ESS Final Total Score at Week 8 (ITT; LME)-HARMONY 1BIS

Visit	Placebo N=32	Pitolisant N=66
Baseline (BL)*		
N	32	66
Mean ± SD	18.2 ±2.3	18.3 ±2.4
Final (F)** at Week 8		
N	32	66
LS Mean† ± SE	15.49±1.32	13.30 ±1.19
p-value		0.03
LS mean differences ± SE		-2.19 ±0.99
95% CI for differences		(-4.17, -0.22)

Source: Table 16 of Sponsor's Clinical Study Report (Page 80)
(BL)* = ESS (V2+V3)/2; Final (F)** = ESS (sum of the last two available values post-baseline)/2; CI = confidence interval; LS = least-squares; LME = mixed model repeated measures; SE = standard error; ITT = Intention to Treat; SD= Standard Deviation; †= The primary analysis was conducted using a linear mixed effects model (LME), featuring analysis of covariance ANCOVA on final ESSf adjusted on ESSb, with treatment considered as a fixed factor and re-allocated center as a random effect (thus hypothesis of center variability of the model intercept)
Note: Increase in ESST total score indicates increased chance of dozing.

Non-inferiority was not achieved for pitolisant (Table 27).

Table 29: Adjusted ESS Final Total Score at Week 8 (ITT; LME)-HARMONY 1BIS

Visit	Modafinil N=65	Pitolisant N=66
Baseline (BL)*		
N	65	66
Mean ± SD	18.1 ±2.8	18.3 ±2.4
Final (F)** at Week 8		
N	65	66
LS Mean† ± SE	10.59 ±1.08	13.34 ±1.08
p-value		0.002
LS mean differences ± SE		-2.75 ±0.87
95% CI for differences		(-4.48, -1.02)

Source: Table 16 of Sponsor's Clinical Study Report (Page 80)
(BL)* = ESS (V2+V3)/2; Final (F)** = ESS (sum of the last two available values post-baseline)/2; CI = confidence interval; LS = least-squares; LME = mixed model repeated measures; SE = standard error; ITT = Intention to Treat; SD= Standard Deviation; †= The primary analysis was conducted using a linear mixed effects model (LME), featuring analysis of covariance ANCOVA on final ESSf adjusted on ESSb, with treatment considered as a fixed factor and re-allocated center as a random effect (thus hypothesis of center variability of the model intercept)
Note: Increase in ESST total score indicates increased chance of dozing.

The per-protocol based sensitivity analyses and supportive analyses (Section 3.2.2.3) were comparable to the primary efficacy analysis.

<u>ESS Responder Rate</u>: ESS ≤ 10

The difference in responder rates between pitolisant and placebo groups were evaluated using Poisson regression analysis adjusting for baseline ESS value and center as random effect. The

response proportion for pitolisant group (65.2%) was statistically greater than the placebo group (34.4%) where estimated relative risk was 2.14 [95% CI (1.35, 3.39); p = 0.001]. Analysis result based on logistic regression was consistent.

There was a statistically significant difference in the ratio of the mean change in MWT (Final/Baseline) between pitolisant and placebo (Student's t-test) [1.46; 95% CI: (1.06, 2.01); p = 0.022].

Reviewer's Note: Both endpoints, MWT and SART, were analyzed using a linear fixed effect model on log (F/BL) with treatment as fixed effect and re-allocated center as random effect (CSR, page 82). The Mann-Whitney and Student's t-test results on MWT were not statistically significant and not consistent with the results of the specified linear fixed effect model.

Table 30: Summary of Analysis Results for Secondary Endpoints (ITT)-HARMONY 1BIS

ITT (N=163)								
Endpoint		PLACEBO (N=32)		PITOLISANT (N=66)		MODAFINIL (N=65)	
		BL	FINAL	BL	FINAL	BL	FINAL
ESS(1) Responder	% (n)	34.4 (11)		65.2 (43)		76.9 (50)	
	RR	2.14 [1.35; 3.39] p = 0.001				0.87 [0.74; 1.02] p = 0.086	
MWT(2)	Value	8.31	8.28	7.34	9.10	7.01	10.90
	F/BL	0.99		1.24		1.55	
	Treat	1.46 [1.06; 2.01] p = 0.022				0.85 [0.66; 1.09] p = 0.205	
SART-NOGO(2)	Value	7.53	7.76	8.21	6.73	8.88	6.50
	F/BL	1.03		0.82		0.73	
	Treat	0.77 [0.65; 0.91] p = 0.002				1.08 [0.93; 1.26] p = 0.294	
SART-GO(2)	Value	3.05	2.60	3.23	2.71	2.94	2.33
	F/BL	0.85		0.84		0.79	
	Treat	0.99 [0.77; 1.27] p = 0.910				1.06 [0.82; 1.37] p = 0.641	
SART - TOTAL(2)	Value	10.54	9.94	11.08	8.90	11.71	8.44
	F/BL	0.94		0.82		0.74	
	Treat	0.83 [0.69; 0.99] p = 0.043				1.08 [0.90; 1.30] p = 0.407	

Source: Table 17 of Sponsor's Clinical Study Report (Page 84)

(1) Responder rate according to ESS (ESSf≤ 10 or ESS (F – BL) ≥ 3) was documented by the responder proportion (%) and treatment group sample size (n). Analysis was conducted using a Poisson regression model on final ESSf adjusted on ESSb, with treatment considered as a fixed factor and center as a random effect. Original SAR displayed placebo vs BF and BF vs modafinil, this analysis displays Pitolisant vs Placebo and Pitolisant vs modafinil.

(2) Mean Wakefulness Time (MWT), SART-nogo, SART-go, and SART total values are documented by **value** (geometric mean at baseline and final time), **F/B** (ratio of Final on Baseline values in each group, **treat** (the ratio F/B between BF and the compared treatment), and **treat** (tested treatment effect using linear fixed effect model with 95%CI and p value).

Reviewer's Note: 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 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 unbinding of study.

APPENDIX A. CLUSTERING OF CENTERS

Source: Applicant's SAP (Page 11)

3.3 Evaluation of Safety

Safety evaluation was not conducted in this review.

4 FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

No special subgroups were investigated.

4.1 Gender, Race, Age, and Geographic Region

The majority of participants were white (94.7%), age group <=65 (98%) in HARMONY 1. Similarly, most participants were also whites (86.7%), age group <=65 (90.3%). Below subgroup exploration by sex was conducted for HARMONY 1 and HARMONY CTP.

The efficacy conclusion in the general population is consistent with the female subgroup in HARMONY 1. Estimated treatment effect of subgroups by sex weren't demonstrably inconsistent in HARMONY CTP.

Table 31: Subgroup Analysis by Sex (HARMONY 1; ITT; LME)

Male			
Visit	Placebo N=30	Pitolisant N=31	Pitolisant-Placebo 95% CI for Differences
Final (F)** at Week 8			
N	13	21	
LS Mean ± SE	13.40±1.61	12.31 ±1.40	-1.09; (-5.19, 3.01)

Female			
Visit	Placebo N=30	Pitolisant N=31	Pitolisant-Placebo 95% CI for Differences
Final (F)** at Week 8			
N	17	11	
LS Mean ± SE	17.63±1.33	11.90 ±1.52	-5.73; (-9.85, -1.62)

Source: Reviewer
Final (F)** = ESS (sum of the last two available values post-baseline)/2; CI = confidence interval; LS = least-squares; LME = linear mixed effect model; SE = standard error

Table 32: Subgroup Analysis by Sex (HARMONY CTP)

Male (N=61)					**Ratio of geometric mean**		
ITT- LOCF method with the average of the last 2 available values							
Analysis	**Estimate**	**SE***	**95% LCL**	**95% UCL**	**Exp† Estimate**	**Exp* LCL**	**Exp* UCL**
Poisson	-0.84	0.12	-1.09	-0.59	**0.43**	**0.34**	**0.56**

Female (N=56)					**Ratio of geometric mean**		
ITT- LOCF method with the average of the last 2 available values							
Analysis	**Estimate**	**SE***	**95% LCL**	**95% UCL**	**Exp† Estimate**	**Exp* LCL**	**Exp* UCL**
Poisson	-0.55	0.12	-0.80	-0.29	**0.58**	**0.45**	**0.75**

Source: Reviewer

4.2 Other Special/Subgroup Populations: U.S. versus Non-US

All the studies were conducted outside of the U.S.

5 SUMMARY AND CONCLUSIONS

5.1 Statistical Issues

Due to lack of thorough prior interactions or agreements with the applicant, we had to request clarifications on a range of issues such as endpoints, efficacy analysis methods for the primary or secondary endpoints.

In HARMONY 1, additional analysis was explored on a secondary endpoint: a subgroup of patients with a history of cataplexy. There was no prospectively planned correction for multiplicity to control the overall type I error rate for these secondary endpoints in this study. Moreover, in this subgroup of patients, the reduction in mean daily rate of cataplexy (p=0.034 without multiplicity adjustment) was based on a specific imputation method for subjects with zero or missing cataplectic events. The confirmatory findings depended on how the missing data were handled.

5.2 Collective Evidence

A total of three (3) efficacy studies were submitted – 2 studies (HARMONY 1, HARMONY 1BIS) to support for the treatment of excessive daytime sleepiness (EDS) in adult patients with narcolepsy; 1 study (HARMONY CTP) for the treatment of cataplexy in adult patients with narcolepsy.

The primary endpoint, ESS final score at the end of treatment period, in HARMONY 1 and HARMONY 1BIS, pitolisant demonstrated statistically significant separation from placebo when adjusted for baseline scores. Significance of the primary endpoint in HARMONY 1BIS was achieved after a random grouping of the small study centers within larger centers. The estimated treatment difference was at least 3 units in HARMONY 1 and 2 units in HARMONY 1BIS. For study HARMONY 1BIS, pitolisant showed a separation from placebo on the ESS endpoint (p-value = 0.03). The result was obtained by "artificially clustering" small clinical study centers into 5 clusters which was specified in the SAP before data unblinding, having learned the potential effect of sparse of data in clinical centers from HARMONY 1.

Pitolisant statistically significantly reduced risk of cataplectic events compared to placebo in HARMONY CTP (rate ratio: 0.51, $p < 0.0001$).

5.3 Conclusions and Recommendations

European Medicines Agency (EMA) recommended a maximum daily oral dose of 36 mg of Wakix for the treatment of narcolepsy with or without cataplexy in the European Union (EU). The Applicant is seeking to get an approval on similar dose (35.6 mg) in the US for two indications, 1) the treatment of excessive daytime sleepiness (EDS) in adults with narcolepsy (supported by HARMONY 1, HARMONY 1BIS); 2) the treatment of cataplexy in adults with narcolepsy (supported by HARMONY CTP).

Efficacy results from HARMONY 1 and HARMONY 1BIS showed improved daytime sleepiness which supports the indication of EDS. The cataplectic claim is supported by results from HARMONY CTP and additional post-hoc analysis results on the daily rate of cataplexy (DRC) in HARMONY 1 on a subgroup of patients with a history of cataplexy. The Applicant generated supportive evidence from HARMONY 1; however, the analysis was post-hoc and the overall type I error rate was not controlled. In addition, this post-hoc analysis which is based on outcome-defined subgroups (exposed-population based on cataplexy events) violates the randomization principle and there is very likely to be imbalances in known and unknown covariates confounding the observed treatment differences. This may lead to invalid statistical comparisons. From statistical point of view, there appears to be only one successful trial supporting the indication of cataplexy.

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