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

Jean-Louis Pépin, Ognian Georgiev, Rumen Tiholov, Valérie Attali, Johan Verbraecken, Bertien Buyse, Markku Partinen, Ingo Fietze, Georgi Belev, Dejan Dokic, et al.

Word count: main text 3410; abstract 258

Pitolisant for residual excessive daytime sleepiness in Obstructive Sleep Apnea patients adhering to Continuous positive Airway Pressure: A randomized trial

Short title: Pitolisant in OSA patients adhering to CPAP

Jean-Louis Pépin[1], Ognian Georgiev[2], Rumen Tiholov[3], Valérie Attali[4], Johan Verbraecken[5], Bertien Buyse[6], Markku Partinen[7], Ingo Fietze[8], Georgi Belev[9], Dejan Dokic[10], Renaud Tamisier[1], Patrick Lévy[1], Isabelle Lecomte[11], Jeanne-Marie Lecomte[11], Jean-Charles Schwartz[11], Yves Dauvilliers[12]. On behalf of the HAROSA I study group.

[1]*HP2 laboratory, INSERM U1042, University Grenoble Alpes; and EFCR Laboratory, Grenoble Alpes University Hospital, Grenoble, France*

[2]*Alexandrovska Hospital Medical University, Department of Internal Medicine, Pulmonology, Sofia, Bulgaria*

[3] *Department of Internal Diseases, Sv. Ivan Rilski Multiprofile Hospital for Active Treatment, Kozloduy, Bulgaria*

[4]*Neurophysiologie Respiratoire Expérimentale et Clinique UMRS1158, Sorbonne Université, INSERM; and Service des Pathologies du Sommeil (Departement R3S, DMU APPROCHES), Groupe Hospitalier Universitaire APHP-Sorbonne Université, Paris, France.*

[5]*Universitair Multidisciplinair Slaap Centrum, Edegem-Antwerp, Belgium*

[6]*Leuvens Universitair Centrum voor Slaap-en waakstoornissen, Department of Respiratory Diseases, University Hospitals Leuven and KU Leuven, Belgium*

[7]*Helsinki Sleep Clinic, Vitalmed Research Center, Department of Clinical Neurosciences, University of Helsinki, Finland*

[8]*Interdisziplinares Schlafmedizinisches Zentrum, Charité - Universitätsmedizin Berlin, Germany*

[9]*Pulmonology, Department of Internal Medicine, St George Hospital Medical University, Plovdiv, Bulgaria*

[10]*Department of Pulmology and Allergy, Mother Teresa Medical University, Macedonia*

[11]*Bioprojet, Paris, France*

[12] *Centre National de Référence Narcolepsie, Unité du Sommeil, CHU Montpellier, Hôpital Gui-de-Chauliac, Service de Neurologie, Université de Montpellier, INSERM U1061, Montpellier, France*

Corresponding author:

Pr. Jean-Louis Pépin, Laboratoire EFCR, CHU de Grenoble Alpes, CS10217, 38043, Grenoble, France; Phone: +33 4 76 76 87 66 ; Email: JPepin@chu-grenoble.fr

Funding: Bioprojet, Paris, France

Summary of conflict of interest statements:

Y.Dauvilliers has consulted for UCB Pharma, Jazz, Theranexus, Flamel, Idorsia, Takeda, Harmony Biosciences, and Bioprojet
Dr. Pépin reports other from Bioprojet, other from Jazz Pharmaceuticals, other from Idorsia, during the conduct of the study. Grants from Air Liquide Foundation , grants and personal fees from Agiradom, grants and personal fees from AstraZeneca, grants from Fisher and Paykel, grants from Mutualia, grants and personal fees from Philips, grants and personal fees from Resmed, grants from Vitalaire, grants from Boehringer Ingelheim, grants from Jazz Pharmaceuticals, grants from Night Balance, grants from Sefam, all outside the submitted work.
Dr. Verbraecken reports grants from Antwerp University Hospital, during the conduct of the study; and grants from Bioprojet, grants from Jazz Pharmaceuticals, grants from UCB Pharma, outside the submitted work.
Dr. Buyse reports no grants or fees during the conduct of the study, but received reimbursement fees for travel and conference expenses from VitalAire, outside the submitted work.
Dr. Tamisier reports other from Agiradom (Healthcare provider) and grants from Resmed, both outside the submitted work.
Drs. Schwartz and JM Lecomte are co-founders, shareholders of Bioprojet pharma and Bioprojet biotech.
Dr. I Lecomte is an employee of Bioprojet pharma.
Drs. Georgiev, Tiholov, Attali, Partinen, Fietze, Belev, Dokic, and Lévy have nothing to disclose.

Prior abstract publication or presentation at a meeting: None

"Take home" message
Study Question: Is pitolisant efficacious and safe in reducing daytime sleepiness in patients presenting with moderate to severe OSA adhering to CPAP treatment but having residual Excessive Daytime Sleepiness?
Results: In a 12 week randomized controlled trial excessive Daytime Sleepiness was significantly reduced with pitolisant compared to placebo. No cardiovascular or other significant safety concerns were reported during this study period.
Interpretation: Pitolisant can be safely used as adjunct to CPAP therapy in OSA patients with residual sleepiness despite good CPAP adherence, to reduce daytime sleepiness.

Abbreviations List

AHI	Apnea + hypopnea index
BDI	Beck Depression Inventory
BMI	Body Mass Index
BOCF	Baseline observation carried forward
CGI-S	Clinical Global Impressions of Severity
CGI-C	Clinical Global Impressions of Change
CPAP	Continuous positive airway pressure
ECG	Electrocardiogram (ECG)
EDS	Excessive daytime sleepiness
EMA	European Medical Agency
ESS	Epworth Sleepiness Scale
ITT	Intention to treat
LOCF	Last Observation Carried Forward
LSEQ	Leeds Sleep Evaluation Questionnaire
MMSE	Mini Mental State Examination
OSA	Obstructive sleep apnea
OSleR	Oxford Sleep Resistance Test
PGO	Patient's Global Opinion
PP	Per-protocol population
SAF	Safety population
SD	Standard deviation
TEAE	Treatment-emergent adverse event
TMT	Trail Making Test

Abstract

Background: Excessive daytime sleepiness (EDS) in individuals with obstructive sleep apnea syndrome persisting despite good adherence to continuous positive airway pressure (CPAP) is a disabling condition. Pitolisant is a selective histamine H3-receptor antagonist with wake-promoting effects.

Research Question: Is pitolisant efficacious and safe in reducing daytime sleepiness in individuals presenting moderate to severe OSA adhering to CPAP treatment but having residual EDS?

Study Design and Methods: In a multicenter, double-blind, randomized (3:1), placebo-controlled, parallel-design trial, pitolisant was individually titrated at up to 20 mg/day and taken over 12 weeks. The primary endpoint was change in the Epworth Sleepiness Scale (ESS) score in intention to treat. Key secondary endpoints were maintenance of wakefulness assessed by the Oxford Sleep Resistance Test (OSleR), clinical global impressions of severity, the patient's global opinion, EQ-5D quality-of-life, Pichot Fatigue questionnaire scores and safety.

Results: 244 OSA participants (82.8% male; mean age: 53.1 years, mean apnea+hypopnea index under CPAP: 4.2/hour, baseline ESS score: 14.7, were randomized to pitolisant (n=183) or placebo (n=61). ESS significantly decreased with pitolisant compared to placebo -2.6 (95%CI: [-3.9;-1.4]) ($p<0.001$) and the rate of responders to therapy (ESS≤10 or ΔESS≥3) was significantly higher with pitolisant (71.0% vs 54.1%; p=0.013). Adverse event occurrence (mainly headache and insomnia) was higher in the pitolisant group compared to the placebo group (47.0% and 32.8%, p=0.03). No cardiovascular or other significant safety concerns were reported.

Interpretation: Pitolisant used as adjunct to CPAP therapy for OSA with residual sleepiness despite good CPAP adherence significantly reduces subjective and objective sleepiness and improves participant-reported outcomes and physician-reported disease severity.

Clinical trial registration: clinicaltrials.gov NCT01072968; EudraCT N°: 2009-017251-94

Key words: Obstructive Sleep Apnea, residual Excessive Daytime Sleepiness, Continuous Positive Airway Pressure, pitolisant

Introduction

Obstructive sleep apnea (OSA) affects up to one billion people worldwide and constitutes a major health concern as it results in multi-organ consequences.[1-3] Excessive daytime sleepiness (EDS) is the dominant complaint for the majority of OSA patients and is often associated with fatigue, impaired attention and vigilance, irritability and depressive symptoms. This impairment in daily functioning results in considerable economic and societal burdens with loss of productivity at work, deterioration in quality-of-life, and an increased risk of accidents.[4,5]

Continuous positive airway pressure (CPAP) is the primary treatment for symptomatic moderate to severe OSA, efficacious in suppressing pharyngeal collapse during sleep and thus normalizing oxygen saturation and sleep quality and architecture. CPAP reduces daytime sleepiness, and improves alertness, cognitive function, and quality-of-life in optimally adherent patients.[2,6,7] However, despite well managed CPAP therapy, residual EDS is reported in 6 to 15% of CPAP-treated OSA.[8,9] Besides CPAP adherence, residual EDS requires appropriate management including good sleep hygiene. Other sleep disorders and depression should be assessed before considering pharmacological therapy with stimulants.[10]

Several wake-promoting agents such as modafinil/armodafinil and more recently solriamfetol as adjunct to CPAP therapy have shown significant improvement in residual sleepiness in randomized controlled trials.[11,12] Solriamfetol has been approved for treatment of residual sleepiness in individuals with OSA in the US and in Europe. The European Medical Agency (EMA) has removed the indication for modafinil due to potential cardiovascular safety concerns.

Pitolisant is a novel selective histamine H3 receptor antagonist/inverse agonist with strong wake-promoting effects that is well tolerated in patients with narcolepsy.[13-15] We recently reported that pitolisant significantly reduced self-reported daytime sleepiness and fatigue, and improved patient-reported outcomes and physician disease severity assessment in the specific phenotype of sleepy individuals with OSA refusing or non-adherent to CPAP.[16] The evaluation of pitolisant needs to be completed in the different subgroup of OSA individuals, those exhibiting residual sleepiness despite good adherence to CPAP treatment.

The objectives of the present study were to demonstrate the efficacy and safety of pitolisant given at 5, 10, or 20 mg once per day versus placebo, during 12 weeks for the treatment of residual EDS in individuals on well-managed CPAP therapy for moderate to severe OSA.

Methods

Study design

This phase 3, double-blind, placebo-controlled, parallel-group multicenter trial evaluated the efficacy and safety of pitolisant over 12 weeks in adults with moderate to severe OSA treated by CPAP for at least 3 months, with at least 4-hour of nightly CPAP usage, residual EDS (Epworth Sleepiness Scale (ESS) score ≥12), and without unstable cardiovascular disease as judged by the investigator. The study was conducted in 35 sleep centers in 9 European countries between August 12, 2011 and June 21, 2013.

The study protocol was approved by the institutional review board or ethics committees of each study site; the study was conducted in accordance with the principles of the Declaration of Helsinki and registered on clinicaltrials.gov (identifier NCT01071876] and EudraCT (n°: 2009-017248-14). All participants provided written informed consent prior to inclusion.

Participants

Included participants were adults with OSA diagnosed according to the International Classification of Sleep Disorders-2 criteria and treated with CPAP for at least 3 months with persistence of EDS despite mean nightly CPAP usage ≥4h. Only individuals assessed by polysomnography under CPAP before inclusion or during the previous year with an apnea + hypopnea index (AHI) ≤10/hour of sleep and EDS, defined as an ESS score ≥ 12, were eligible for inclusion. Additional inclusion criteria were a Periodic Limb Movement Disorder arousal index (PLMAI) ≤ 10 per hour, a 13-item Beck Depression Inventory (BDI-13) score < 16 and item G (suicidal ideation) =0, a Mini Mental State Examination (MMSE) score ≥ 28, and a Body Mass Index (BMI) ≤ 40 kg/m² (owing to the risk of obesity hypoventilation syndrome and because morbid obesity might be a significant cause for sleepiness).

Key non-inclusion criteria were: history of a medical disorder other than OSA associated with EDS (such as severe chronic insomnia, narcolepsy, restless legs syndrome, sleep deprivation, night-time or shift work); previous surgical intervention for OSA including uvulopalatopharyngoplasty (UPPP); use of a mandibular advancement device; current or recent history of drug, alcohol, or other substance abuse or dependence; history or presence of an unstable or clinically significant medical condition especially those related to the cardiovascular system (recent myocardial infarction, angina, arterial hypertension or dysrhythmia, ECG - Bazett's corrected QT interval higher than 450 ms, history of left ventricular hypertrophy or mitral valve prolapse), a psychiatric disorder, or a condition that could affect safety or interfere with study assessments; pregnancy or breast feeding; and/or the use of any treatment that could affect the evaluation of EDS.

Randomization and masking procedures

Procedures were similar to the companion study.[16] Randomization was centralized and performed via a website (Arone Projection; https://www.bioprojet-studies.org/). Randomization was on a 3:1 (three pitolisant for one placebo) basis (details in supplemental material). Pitolisant and placebo were contained within sealed capsules, similar in appearance and taste, and containing a one-fourth (5mg), one-half (10 mg), or one full tablet of pitolisant (20 mg) or lactose only (placebo). The participants, their sleep/respiratory physicians, study investigators and all research staff were masked to the treatment allocation.

Intervention

Treatment was taken once a day on an empty stomach within 1 hour of waking-up. The individual titration began with 5 mg/day during 1 week, then 10 mg/day was proposed during 1 week and then 20 mg during 1 week if necessary, based on efficacy and tolerability. The best adapted and tolerated dose was administered for the 9 week stable dose period (Figure 1).

Outcomes

The primary efficacy endpoint was change in ESS score from baseline to the end of treatment at week 12.

The key secondary endpoint was change from baseline to week 12 in the Oxford Sleep Resistance Test (OSleR), which objectively measures ability to maintain vigilance. This consisted of three 40min sessions of sleep-resistance challenges at approximately 9:00 am, 11:00 am and 1:00 pm. The mean sleep latency and the number of errors (3 to 6 consecutive errors indicating micro-sleep and ≥7 errors indicating sleep onset) were collected.[16,17] Other secondary endpoints were: responders by other ESS criteria (ESS≤10 or improvement ≥3 points (ΔESS≥3), episodes of sleepiness and daytime sleep recorded in sleep diaries (see online supplement protocol amendments for details of sleep diary data collection), parts A&B of the Trail Making Test (TMT), the clinicians' Clinical Global Impressions of Severity and Change (CGI-S and CGI-C), the Patient's Global Opinion (PGO), the Leeds Sleep Evaluation Questionnaire (LSEQ), EuroQoL (EQ-5D) quality-of-life questionnaire, and the Pichot Fatigue scale.

Safety was assessed through clinical adverse events (AEs), clinical laboratory parameters (hematology, biochemistry, and electrolytes), vital signs, physical examination, electrocardiogram (ECG), BDI-13 scale, amphetamine-like withdrawal symptoms, and the patient's overall evaluation of tolerance. Blood pressure measurements were conducted following recommendations of European Society of Cardiology with at least 2 measurements taken at each assessment, both after 15 min in a supine position.

Statistical analysis

The statistical analysis plan was the same as for the companion study.[16]

Sample size calculation

Exploratory study results indicated residual ESS variability with a standard deviation (SD) of 6 points. Before the study the investigators agreed on a Minimum Important Difference (MID) in ESS = −3 corresponding to an effect size (ES) of 0.5. Recent independent studies,[17,18] have established the MID ESS to lie between −2 and −3. The correlation between final and baseline ESS was conservatively estimated as r = −0·4. Assuming an ANCOVA 95% confidence interval (CI) for the main confirmatory test, a difference of >3 points should be detected with a power of 90% by including at least 60 participants in the placebo group and 180 in the pitolisant group.

Description of the study populations

The Intention-to-Treat (ITT) population included all randomized participants. The Safety population (SAF) was all participants who received at least one dose of study medication irrespective of the outcome, and for whom at least one valid post-baseline evaluation (including any AE) was available. The Per Protocol (PP) population included ITT participants without any major protocol violations and who did not prematurely discontinue the study drug or placebo during the 12-week treatment phase of the study.

The PP population was determined by a blinded review of the data prior to database lock. Demographic data and other baseline characteristics were analyzed using the ITT population. Efficacy was analyzed for both the ITT and PP populations, with the ITT population analysis considered the primary analysis. Safety, concomitant medications, exposure, dosing, and compliance were analyzed using the Safety population.

The statistical analysis was done by an independent external statistician. Another third party statistician independently reviewed the results. Descriptive statistics were used for the quantitative variables, and frequency distribution for the ordinal and nominal variables. Exact 95%CI are given for selected variables.

The final ESS score was compared using a linear mixed effects model, considering treatment as a fixed factor, center as a random factor, and ESS and BMI at baseline as adjustment covariates. The ESS score could be log transformed if necessary, depending upon normality of the residuals. The analysis of safety data was descriptive except for comparisons of the frequencies of participants with treatment-emergent adverse events (TEAEs) by logistic regression. Missing data for the primary efficacy variable and for response were allocated using the Last Observation Carried Forward (LOCF) method. A sensitivity analysis was performed using the baseline ESS value carried forward (BOCF) adjusting for ESS and Body Mass Index (BMI) at baseline.

This trial was conducted considering a single primary endpoint (ESS) associated with the ITT dataset, with one test comparing pitolisant with placebo via one main statistical analysis (ANCOVA). All statistical tests were two-sided, at a 5% level of significance.

Results

Participants

We screened 298 individuals for inclusion, of which 244 (82%) were retained for the double-blind phase of the study and randomized to either pitolisant (n=183) or placebo (n=61) (Figure 2 and e-table 1). All 244 participants received at least one dose of study medication and had a validated post-baseline assessment. In this safety population 36 had at least one major protocol deviation (e-table 2), and 12 participants discontinued the study prematurely (4 of them had also a major deviation). The PP population was 200 participants, 148 in the pitolisant and 52 in the placebo groups.

The ITT population was primarily male (82.8%), with a mean age of 53.1 (SD: 10.6) years. Mean AHI under CPAP was 4.2 (SD: 3.5)/h, and mean CPAP pressure 10.7cm (SD: 2.8) H_2O. No significant differences in demographic or clinical characteristics were found between the treatment groups (Table 1).

Primary efficacy endpoint

The ESS geometric mean was 14.9 $\pm$ 2.7 at baseline and decreased to 9.0 $\pm$ 4.8 at the end of the 12-week intervention in the pitolisant group. In the placebo group, the ESS geometric mean decreased from 14.6 $\pm$ 2.8 to 12.1 $\pm$ 6.1. The change in ESS from baseline to end of treatment was -5.5 (95%CI [-6.2; -4.9]) in the pitolisant group and -2.8 (95%CI [-4.3; -1.2]) in the placebo group ($p<0.001$). There was a significant difference between the two arms in favor of pitolisant: -2.6 (95%CI: [-3.9; -1.4]) ($p<0.001$) (Figure 3, Table 2). Pre-specified sensitivity analyses adjusting for BMI and ESS at baseline did not change the results.

Secondary efficacy outcomes

Pitolisant resulted in normalization of the ESS score (ESS≤10) in 56.3% of participants versus 42.6% in the placebo group ($p=0.028$). ESS response defined as either ESS≤10 or improvement ≥3 points was observed in 71.0% and 54.1% in the pitolisant and placebo groups respectively (Table 2).

Baseline OSleR mean sleep latencies (mean (range)) were 15.5 (0.3;40.0) and 19.0 (0.7;40.0) minutes for pitolisant and placebo groups, respectively. The ratio of increase in mean latency during OSleR Tests was 1.4 in the pitolisant and 1.2 in the placebo group ($p=0.050$ using a mixed model for repeated measures) (Table 3). Similar results were found in the PP analysis. There was a trend towards an improvement in sleep diary variables in the pitolisant group compared to placebo regarding the number of sleep/sleepiness episodes, $p=0.06$. No

between-group differences were found regarding EQ-5D. In the Leeds questionnaire, 2 items were significantly improved in the pitolisant arm: “getting to sleep” (participants had less propensity to fall asleep p=0.020) and “quality of sleep” (p=0.05). There were no changes in mean time to perform parts A or B of the Trail Making Tests. At the end of the double-blind phase the CGI had improved for 78% of the pitolisant group compared to 53.4% of the placebo group (p<0.001). Improvement in the PGO endpoint was perceived by 76.4% of the participants in the pitolisant group compared to 56.9% on placebo (p=0.005).

The mean Pichot Fatigue Scale score decreased in both pitolisant and placebo groups (13.2±7.2 to 9.4±6.9, 11.4±7.2 to 8.6±6.0 respectively) without significant between-group difference (Table 3). During the double-blind phase, the maximum dose was 20 mg/day for 79.8% of participants in the pitolisant and 88.5% in the placebo group.

Safety

Safety evaluation was based on the incidence of TEAEs: 47.0% in the pitolisant and 32.8% in the placebo group (p=0.03). The most frequently reported TEAE was headache (14.8% and 11.5% for pitolisant and placebo respectively). Insomnia was reported in a higher proportion of participants treated with pitolisant (9.3%) than with placebo (3.3%) (Table 4). The frequency of treatment-related TEAEs was similar (headache, insomnia, diarrhea) and did not differ between groups (26.8 % with pitolisant and 19.7% with placebo; p=0.256). The frequency of severe treatment-related TEAEs was similar in both treatment groups (pitolisant: 27%; placebo: 32.8%).

TEAEs leading to study drug withdrawal were reported for 4 participants (2.2%) in the pitolisant group, and for 2 (3.3%) in the placebo group. Treatment-emergent SAEs were reported for 2 participants during pitolisant treatment (1.1%, irritable bowel syndrome and musculoskeletal pain; both were considered unlikely to be treatment-related), and in none on placebo.

None of the participants experienced dysphoria, or vivid and unpleasant dreams during the placebo wash-out one week after treatment termination. BDI scores, blood chemistry and hematological or cardiovascular parameters did not change significantly in either group.

During treatment, there were no changes from baseline in systolic and diastolic blood pressure (BP) or heart rate for either group (Figure 4, Table 4). Mean values of ECG variables were comparable in the two treatment groups. However, in the pitolisant group, 4

participants (2.2%) had at least one post-dose QTcF > 450 msec and 6 patients (3.3%) had one QTcF elongation ≥ 60 msec, while there were 2 participants (3.3%) with QTcF > 450 msec and 3 (4.9%) with QTcF elongation ≥60msec in the placebo group.

Discussion

In this large randomized controlled trial, residual excessive daytime sleepiness in individuals with OSA and adherent to CPAP was significantly improved with pitolisant. Such an improvement was reported both subjectively by a -2.6 (95%CI: [-3.9; -1.4]) reduction in ESS and objectively by the OSleR maintenance of wakefulness test. These results were in agreement with an overall improvement in both patient-reported outcomes and physician assessed severity of EDS.

ESS is a patient-reported outcome that assesses propensity to fall asleep in different everyday situations, while the OSleR test is an objective measure of the subject's ability to maintain wakefulness. Both types of assessment were consistent in demonstrating the superiority of pitolisant over placebo. Variations in ESS and OSleR sleep latencies were not explained by sleep duration, being 7.2 $\pm$ 0.9 and 6.9 $\pm$ 1.3 hours in the pitolisant and placebo groups respectively throughout the study, excluding chronic sleep deprivation. Some OSleR assessments (type and number of errors) reflecting micro-sleep episodes occurring during the tests did not differ significantly between groups. This might be related to a ceiling effect as a large proportion of included participants already exhibited normal values at baseline (23.6 % had mean sleep latency ≥30 minutes in the pitolisant group and 33.3 % in the placebo group).

One strength of our study was to have been conducted in a well-defined phenotype of residual sleepiness persisting in individuals with moderate to severe OSA adherent to CPAP. CPAP adherence at study inclusion was defined as a nightly usage above 4 hours/night. It is now admitted that an increase in adherence to nearer seven hours/night might better control residual EDS.[8] However, the current results nicely complement those reported with pitolisant in another OSA phenotype, patients refusing or not adhering to CPAP.[16] Previous studies in the field evaluating modafinil, armodafinil or solriamfetol have often assessed mixed OSA populations in the same study whether adherent or not to CPAP.[11,12]

In this study the magnitude of improvement in ESS with pitolisant was close to that previously reported in studies of modafinil, armodafinil and solriamfetol in OSA patients. In the present study, the maximum daily dose of pitolisant tested was 20 mg which was used by the majority of participants (79.8% in the pitolisant and 88.5% in the placebo group). This is half the maximum dose tested in narcolepsy studies[13,14] and approved by FDA and by EMA. It is unclear whether higher doses might yield a more impressive benefit on sleepiness.[19] An ongoing study, HAROSA III, is testing this hypothesis [NCT02739568]. However, the true answer in terms of comparison of efficacy merits to be evaluated by head to head comparisons between the different classes of wake-promoting agents. Also, further studies addressing combinations of drugs with different mechanisms of action would be of interest.

Concerning the other secondary outcomes, the superiority of pitolisant was clearly perceived at the end the 12 weeks of double-blind treatment both by physicians through the CGI-C and by participants through the PGO of effect. This optimal improvement of ESS is also observed after 12 weeks in narcolepsy patients.[15] "Residual sleepiness" is not only sleepiness but is associated with a constellation of multidimensional symptoms and neuropsychological dysfunctions[8,20] that can be reversed by appropriate management and certainly justify the implementation of pharmacological therapies.

Our results confirm the overall good safety profile of pitolisant already reported in patients with narcolepsy,[13,14] and observed in patients refusing CPAP.[16] No major changes were found in physical examination parameters or vital signs, depressive symptoms, ECG and laboratory test results during the study. Moreover, no withdrawal symptoms occurred following the abrupt discontinuation of pitolisant. This is consistent with the absence of an abuse-potential signal for pitolisant in preclinical models,[21] other clinical trials[13-16] and in a dedicated study of recreational stimulant abusers.[22] A small significant difference in TEAEs was observed in the pitolisant group. There were no major safety concerns raised during the study. The most frequently reported TEAEs were headache, followed by insomnia, diarrhea and back pain.

The study was conducted in a population of OSA patients in which half had a history of cardiovascular or metabolic diseases. The absence of any signal for elevation of systolic and diastolic blood pressure and heart rate with up to 20mg of pitolisant seems reassuring for its use in such at-risk populations with multimorbidities. In contrast, modafinil/armodafinil was associated with a slight increase in systolic BP of 3.0 mmHg

(95%CI 0.8–5.2 mmHg) and diastolic BP of 1.9 mmHg (95%CI 0.5–3.3 mmHg) in some trials, while there was no change reported in other trials according to a recent meta-analysis.[23] In a recent study using solriamfetol the supratherapeutic dose of 300 mg caused a 2.5 mmHg increase in systolic BP and 1.5 mmHg increase in diastolic BP; and heart rate increased by 2-3 bpm at doses above 75mg. Again, head-to-head comparisons of the different available wake-promoting agents, with particular focus on cardiovascular outcomes are needed.

Our study had many strengths and adds to the literature in a number of important ways, but it also has limitations. The first one is related to the 12-week duration. This double-blind study was followed by a 9-month extension phase in open label to assess both the maintenance of efficacy and safety. CPAP adherence was not systematically collected during the trial, but this is part of the routine follow-up of these patients and study investigators did not report unexpected reductions in CPAP adherence. This outcome should be included in future studies.

In conclusion, in this 12-week, phase 3 randomized placebo controlled clinical trial, pitolisant reduced residual excessive daytime sleepiness in individuals with OSA adherent to CPAP treatment in both subjective (Epworth Sleepiness Scale) and objective (OSleR Test) assessments. This was confirmed by both patient reported outcomes and the physicians' clinical global impressions of efficacy, without any significant safety signal, in particular none regarding cardiovascular parameters. The significance of efficacy and safety is limited to the 12 week period and longer term studies will be needed to assess long term efficacy and safety.

Acknowledgements

We are grateful to the members of HAROSA I study group: Valerie Attali, Sleep Disorder Unit, la Pitié-Salpêtrière Hospital, Paris, France; Patrice Bourgin, Hôpital Civil, Strasbourg, France; Yves Dauvilliers, Sleep Unit, Department of Neurology, Gui-de-Chauliac Hospital, Montpellier, France; Marie D'Ortho, Unité Epreuves Fonctionnelles Respiratoires, Hopital Bichat, Paris, France; Frederic Gagnadoux, Department of pneumology, CHU Angers, France; Jean Claude Meurice, pneumology CHU Poitiers, France; Xuan Lan Nguyen, Saint Antoine Hospital, Paris , France, Jean Louis Pépin, Unité Epreuves Fonctionnelles Respiratoires, Michallon Hospital, La Tronche, France; Bertien Buyse, Leuvens Universitair Centrum voor Slaap- en waakstoornissen, University Hospitals Leuven, Belgium; Katrien Hertegonne, Pneumology polyclinic, Gent, Belgium; Daniel Rodenstein, Pneumology Saint Luc clinic, Brussels, Belgium; Johan Verbraecken, Multidisciplinary Sleep Disorders Centre, Antwerp University Hospital and University of Antwerp, Belgium; Jan Ovesen, Sleep clinical trial Aps, Kodling, Denmark; Soren Berg, Scan Sleep ApS, Sovnlaegecentret, Copenhagen, Denmark; Markku Partinen, Helsinki sleep clinic, Helsinki, Finland; Olli Polo, Unesta Research Center Tampere, Finland; Tarja Saaresranta, sleep research unit, University of Turku, Turku, Finland; Jan Anders Hedner, Sleep medicine clinic Sahlgrenska University Hospital, Gothenburg, Sweden; Yuksel Peker, Sleep medicine unit, Skaraborg county hospital, Skövde, Sweden; Ingo Fietze interdisziplinäres schlafmedizinesches Zentrum, Charité, Berlin, Germany; W.J Randerath, pneumology Institut Witten Herdecke, Solingen, Germany; Elke Rössner, Pneumology and sleep medicine clinic, Nurenberg, Germany; Diego Garcia Borreguero, Sleep research institute, Madrid, Spain; Francisco Javier Puertas Cuesta, Sleep unit Neurophysiology department, Ribera hospital, Valencia, Spain; Joaquim Duran-Cantolla, sleep disorder unit, Txagorritxu hospital , Vitoria Gasteiz, Spain; Ferran Barbe, Vilanova de Lleida, Lleida, Spain; Dra Odile Romero, neurophysiology unit, Vall d'Hebron hospital, Barcelona, Spain; Georgi Belev, Department of pneumology , Saint George Hospital, Plovdiv, Bulgaria; Ognian Georgiev, Department of pneumology, Alexandrovska hospital, Sofia, Bulgaria; Yavor Ivanov, Clinic of pneumology, Pleven, Bulgaria; Hristo Metev, Department of pneumology, Rousse, Bulgaria; Diana Petkova, Department of pneumology, Varna, Bulgaria; Rumen Tiholov, Department of internal diseases, Kozloduy, Bulgaria; Dejan Dokic, Department of pneumology and allergy, Mother Teresa medical university, Skopje, Macedonia; Merita Ismajli Marku, Neuropraxis , Skopje, Macedonia;

We thank Alison Foote (Grenoble Alpes University Hospital, France) for editing the manuscript.

Guarantor statement: Jean-Louis Pépin takes responsibility for the content of the manuscript, including the data and analysis.

Author's contributions: IL and J-ML participated in the conception, design, and organization of the study. YD and J-LP participated in the conception and design of the study, and wrote the paper. J-CS participated in the conception and design, and minor revision to the paper. OG, RTi, VA, JV, BB, MP, IF, GB, DD, RTa and PL were investigators or coordinators of the study and assisted in revising the manuscript.
All authors shared the decision to submit the manuscript for publication.

Summary of conflict of interest statements:
Dr.Dauvilliers has consulted for UCB Pharma, Jazz, Theranexus, Flamel, Idorsia, Takeda, Harmony Biosciences, and Bioprojet;
Dr. Pépin reports other from Bioprojet, other from Jazz Pharmaceuticals, other from Idorsia, during the conduct of the study. Grants from Air Liquide Foundation , grants and personal fees from Agiradom, grants and personal fees from AstraZeneca, grants from Fisher and Paykel, grants from Mutualia, grants and personal fees from Philips, grants and personal fees from Resmed, grants from Vitalaire, grants from Boehringer Ingelheim, grants from Jazz Pharmaceuticals, grants from Night Balance, grants from Sefam, all outside the submitted work;
Dr. Verbraecken reports grants from Antwerp University Hospital, during the conduct of the study; and grants from Bioprojet, grants from Jazz Pharmaceuticals, grants from UCB Pharma, outside the submitted work;
Dr. Buyse reports no grants or fees during the conduct of the study, but received reimbursement fees for travel and conference expenses from VitalAire, outside the submitted work;
Dr. Tamisier reports other from Agiradom (Healthcare provider) and grants from Resmed, both outside the submitted work.

Drs. Schwartz and JM Lecomte are co-founders, shareholders of Bioprojet pharma and Bioprojet biotech.

Dr. I Lecomte is an employee of Bioprojet pharma.

Drs. Georgiev, Tiholov, Attali, Partinen, Fietze, Belev, Dokic, and Lévy have nothing to disclose.

Role of the sponsors:

JCS and JML are co-founders, shareholders of Bioprojet pharma and Bioprojet biotech. IL is an employee of Bioprojet pharma. JCS and JML participated in the conception of the study. IL helped organize the study.

Data sharing statement

Data collected for the study, including deidentified individual participant data and a data dictionary defining each field in the set, will be made available to others following the publication of this article, as well as additional related documents (study protocol, statistical analysis plan, informed consent form) for academic purposes (e.g. meta-analyzes) on request to the sponsor Bioprojet (jm.lecomte@bioprojet.com) and with a signed data access agreement.

References

1. Benjafield AV, Ayas NT, Eastwood PR, et al. Estimation of the global prevalence and burden of obstructive sleep apnoea: a literature-based analysis. *Lancet Respir Med.* 2019;7(8):687-98.

2. Levy P, Kohler M, McNicholas WT, et al. Obstructive sleep apnoea syndrome. *Nat Rev Dis Primers.* 2015;1:15015.

3. McNicholas WT, Bassetti CL, Ferini-Strambi L, et al. Challenges in obstructive sleep apnoea. *Lancet Respir Med.* 2018;6(4):170-2.

4. Bucks RS, Olaithe M, Rosenzweig I, Morrell MJ. Reviewing the relationship between OSA and cognition: Where do we go from here? *Respirology.* 2017;22(7):1253-61.

5. Rosenzweig I, Glasser M, Polsek D, Leschziner GD, Williams SC, Morrell MJ. Sleep apnoea and the brain: a complex relationship. *Lancet Respir Med.* 2015;3(5):404-14.

6. Bratton DJ, Gaisl T, Schlatzer C, Kohler M. Comparison of the effects of continuous positive airway pressure and mandibular advancement devices on sleepiness in patients with obstructive sleep apnoea: a network meta-analysis. *Lancet Respir Med*. 2015;3(11):869-78.

7. Schwartz M, Acosta L, Hung YL, Padilla M, Enciso R. Effects of CPAP and mandibular advancement device treatment in obstructive sleep apnea patients: a systematic review and meta-analysis. *Sleep Breath.* 2018;22(3):555-68.

8. Gasa M, Tamisier R, Launois SH, et al. Residual sleepiness in sleep apnea patients treated by continuous positive airway pressure. *J Sleep Res.* 2013;22(4):389-97.

9. Pepin JL, Viot-Blanc V, Escourrou P, et al. Prevalence of residual excessive sleepiness in CPAP-treated sleep apnoea patients: the French multicentre study. *Eur Respir J.* 2009;33(5):1062-7.

10. Chapman JL, Serinel Y, Marshall NS, Grunstein RR. Residual Daytime Sleepiness in Obstructive Sleep Apnea After Continuous Positive Airway Pressure Optimization: Causes and Management. *Sleep Med Clin.* 2016;11(3):353-63.

11. Schweitzer PK, Rosenberg R, Zammit GK, et al. Solriamfetol for Excessive Sleepiness in Obstructive Sleep Apnea (TONES 3): A Randomized Controlled Trial*. Am J Respir Crit Care Med.* 2019;199(11):1421-31.

12. Strollo PJ, Jr., Hedner J, Collop N, et al. Solriamfetol for the Treatment of Excessive Sleepiness in OSA: A Placebo-Controlled Randomized Withdrawal Study. *Chest.* 2019;155(2):364-74.

13. Szakacs Z, Dauvilliers Y, Mikhaylov V, et al. Safety and efficacy of pitolisant on cataplexy in patients with narcolepsy: a randomised, double-blind, placebo-controlled trial. *Lancet Neurol.* 2017;16(3):200-7.

14. Dauvilliers Y, Bassetti C, Lammers GJ, et al. Pitolisant versus placebo or modafinil in patients with narcolepsy: a double-blind, randomised trial. *Lancet Neurol*. 2013;12:1068-75.

15. Dauvilliers Y, Arnulf I, Szakacs Z, et al. Long-term use of pitolisant to treat patients with narcolepsy: Harmony III Study. *Sleep.* 2019;42(11):174.

16. Dauvilliers Y, Verbraecken J, Partinen M, et al. Pitolisant for Daytime Sleepiness in Obstructive Sleep Apnea Patients Refusing CPAP: A Randomized Trial. *Am J Respir Crit Care Med.* 2020. doi: 10.1164/rccm.201907-1284OC.

17. Crook S, Sievi NA, Bloch KE, et al. Minimum important difference of the Epworth Sleepiness Scale in obstructive sleep apnoea: estimation from three randomised controlled trials. *Thorax*. 2019;74(4):390-6.

18. Patel S, Kon SSC, Nolan CM, et al. The Epworth Sleepiness Scale: Minimum Clinically Important Difference in Obstructive Sleep Apnea. *Am J Respir Crit Care Med*. 2018;197(7):961-3.

19. Trotti LM. Treat the Symptom, Not the Cause? Pitolisant for Sleepiness in Obstructive Sleep Apnea. *Am J Respir Crit Care Med.* 2020. doi: 10.1164/rccm.202001-0104ED.

20. Vernet C, Redolfi S, Attali V, et al. Residual sleepiness in obstructive sleep apnoea: phenotype and related symptoms. *Eur Respir J.* 2011;38(1):98-105.

21. Uguen M, Perrin D, Belliard S et al. Preclinical evaluation of the abuse potential of pitolisant, a histamine H3 receptor inverse agonist/antagonist compared with modafinil. *Br J Pharmacolo.*2013;169(3):632-44.

22. Setnik B, McDonnell M, Mills C et al. Evaluation of the abuse potential of pitolisant, a selective H3-receptor antagonist/inverse agonist for the treatment of adults patients with narcolepsy with or without cataplexy. *Sleep,* 2020;43(4):252. doi: 10.1093/sleep/zsz252

23. Chapman JL, Vakulin A, Hedner J, Yee BJ, Marshall NS. Modafinil/armodafinil in obstructive sleep apnoea:a systematic review and meta-analysis. *Eur Respir J.* 2016;47(5):1420-8.

Figure Legends

Figure 1. Study Design

TC: telephone call; ESS: Epworth Sleepiness score

Figure 2. Patient Flowchart

See online supplement for reasons for non-eligibility (e-table 1) and dose titration details.

Figure 3. Mean change in Epworth Sleepiness Score (ESS) over 12 week double-blind phase, ITT population (N=244)

Figure 4. Heart rate (HR), Systolic (SBP) and Diastolic (DBP) Blood Pressure in pitolisant and placebo groups over 12 week double blind phase

Table 1: Baseline Characteristics

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

AHI: apnea-hypopnea index; BMI: Body mass index; CPAP: continuous positive airway pressure

Table 2: Efficacy results for the primary endpoint: Change in ESS score

Parameter	Pitolisant (N=183)	Placebo (N=61)	P value
ESS score at inclusion Mean (SD)	14.9 (2.7)	14.6 (2.8)	–
ESS score at end of treatment Mean (SD)	9.0 (4.8)	12.1 (6.1)	–
Final ESS score DB-LOCF Mean (SD) 95% CI	9.4 (4.6) [8.8 ; 10.1]	11.9 (5.7) [10.4 ; 13.3]	<0.001
Change in ESS score (DB-LOCF – inclusion Mean (SD) 95%CI	-5.5 (4.4) [-6.2 ; -4.9]	-2.7 (5.9) [-4.3 ; -12.4]	<0.001
ESS ≤10 N (%) 95% CI	103 (56.3%) [48.8% - 63.6%]	26 (42.6%) [30.0% - 55.9%]	0.028
ESS≤10 or reduction in ESS ≥3 N (%) 95% CI	130 (71 %) [63.9% - 77.5%]	33 (54.1%) [40.8% - 66.9%]	0.013

CI: Confidence interval; DB-LOCF: Database with Last Observation Carried Forward; ESS: Epworth Sleepiness Scale; data is presented as means (SD) and confidence intervals.

Table 3: Efficacy results for secondary outcomes

Parameter	Pitolisant (N=183)	Placebo (N=61)	P value
OSleR Test			
OSleR mean sleep latency at inclusion: min (range)	15.5 (0.3-40.0)	18.9 (0.7-40.0)	-
OSleR mean sleep latency at end of treatment: min (range)	22.3 (1.3-40.0)	21.9 (0.7-40.0)	-
Ratio OSL at visit 6 / OSL at visit 2 (Geometric mean)	1.44	1.22	0.05
Sleep Diary variables			
Mean change in number of sleep or sleepiness episodes per day (SD)	-2.1 (1.8)	-1.34 (1.7)	0.06
Mean change in duration of sleep or sleepiness episodes: minutes per day (SD)	-51.8 (69.3)	-47.7 (66.9)	0.70
Pichot Fatigue Score			
Mean Change (SD)	-3.8 (5.6)	-2.9 (5.9)	0.70
Leeds Sleep Evaluation Questionnaire			
Mean change in ease of getting to sleep (SD)	8.4 (20.8)	0.7 (23.7)	0.02
Mean change in quality of sleep (SD)	9.9 (26.6)	15.2 (21.9)	0.05
Mean change in ease of awaking following sleep (SD)	12.1 (24.8)	12.0 (26.2)	0.81
Mean change in behavior following wakening (SD)	15.7 (21.8)	15.7 (22.7)	0.37
Mean change in Global LSEQ score (SD)	11.6 (14.8)	10.9 (14.9)	0.78
Trail Making Test			
TMT part A: Mean change in average time (sec) (SD)	-5.9 (13.0)	-6.2 (13.3)	0.88
TMT part B Mean change in average time (sec) (SD)	-11.7 (37.0)	-15.3 (34.4)	0.45
EQ-5D Mean change in VAS score (SD)	5.5 (14.9)	3.5 (18.9)	0.52
Clinical Global Impression (CGI) N (%)	136 (78.0%)	31 (53.4%)	<0.001
95% CI	71.1% - 84.0%	39.9% - 66.7%	
Very much improved N (%)	19 (11.0%)	4 (6.9%)	
Much improved N (%)	73 (42.2%)	16 (27.6%)	
Minimally improved N (%)	43 (24.9%)	11 (19.0%)	
No change N (%)	33 (19.1%)	18 (31.0%)	
Minimally worse N (%)	5 (2.9%)	8 (13.8%)	
Much worse N (%)	0 (0.0%)	1 (1.7%)	
Patient Global Opinion (PGO): improvement at end of double-blind treatment			
N (%)	133 (76.4%)	33 (56.9%)	0.005
95% CI	69.4% - 82.5%	43.2% - 69.8%	

TMT: Trail Making Test; VAS: Visual Analogue Scale; min: minutes; OSL: OSleR Sleep Latency for OSleR tests. Data is presented as means (SD), means and range for OSleR sleep latencies and number, percentages (%) and with 95% CI for CGI and PGO scales.

Table 4: Safety parameters

Parameter	Pitolisant (N=183)	Placebo (N=61)	P value
Any TEAE	86 (47.0%)	20 (32.8%)	0.030
Any treatment-related TEAE	49 (26.8%)	12 (19.7%)	0.256
Any Serious TEAE	2 (1.1%)	0 (0.0%)	0.998
Any TEAEs leading to study drug withdrawal	4 (2.2%)	2 (3.3%)	0.625
Systolic Blood Pressure, mean (SD)			
At baseline (V2)	129.3 (12.9)	130.2 (11.8)	
Range	100 to 180	110 to 163	
At the end of DB treatment (V6)	128.7 (12.0)	129.1 (12.0)	
Range	98 to 188	110 to 166	
Mean change (SD)	-0.6 (10.1)	-1.8 (10.1)	0.704
Range	-50 to 25	-20 to 33	
Diastolic Blood Pressure, mean (SD)			
At baseline (V2)	80.3 (8.9)	80.6 (6.9)	
Range	56 to 109	59 to 96	
At the end of DB treatment (V6)	79.9 (8.3)	81.4 (9.0)	
Range	52 to 105	67 to 114	
Mean change (SD)	-0.4 (7.3)	0.6 (9.0)	0.228
Range	-25 to 20	-18 to 30	
Heart rate (SD), mean (SD)			
At baseline (V2)	70.9 (11.9)	71.3 (9.6)	
Range	40 to 107	46 to 91	
At the end of DB treatment (V6)	70.0 (11.5)	70.3 (10.4)	
Range	43 to 115	39 to 96	
Mean change (SD)	-0.9 (9.6)	-1.4 (9.1)	0.845
Range	-25 to 29	0	
Total 13 item BDI score			
Mean score at baseline (V2) (SD)	4.5 (3.5)	4.0 (3.4)	
95% CI	[4.0 ; 5.0]	[3.1 ; 4.8]	
Mean score at the end of DB treatment (V6) (SD)	3.3 (3.2)	2.8 (3.1)	
95% CI	[2.9 ; 3.8]	[2.0 ; 3.7]	
Mean change between baseline and end of DB treatment	-1.2 (2.4)	-1.2 (2.0)	0.516
95% CI	[-1.5 ; -0.8]	[-1.8 ; -0.7]	

BDI: Beck Depression Inventory; DB: double blind; TEAE: treatment-emergent adverse event; V2 = visit 2; V6 = visit 6; TEAE are presented as numbers and percentages (%); Blood pressure and heart rate data are presented as means (SD) and ranges; and the 95% CI for BDI scores.

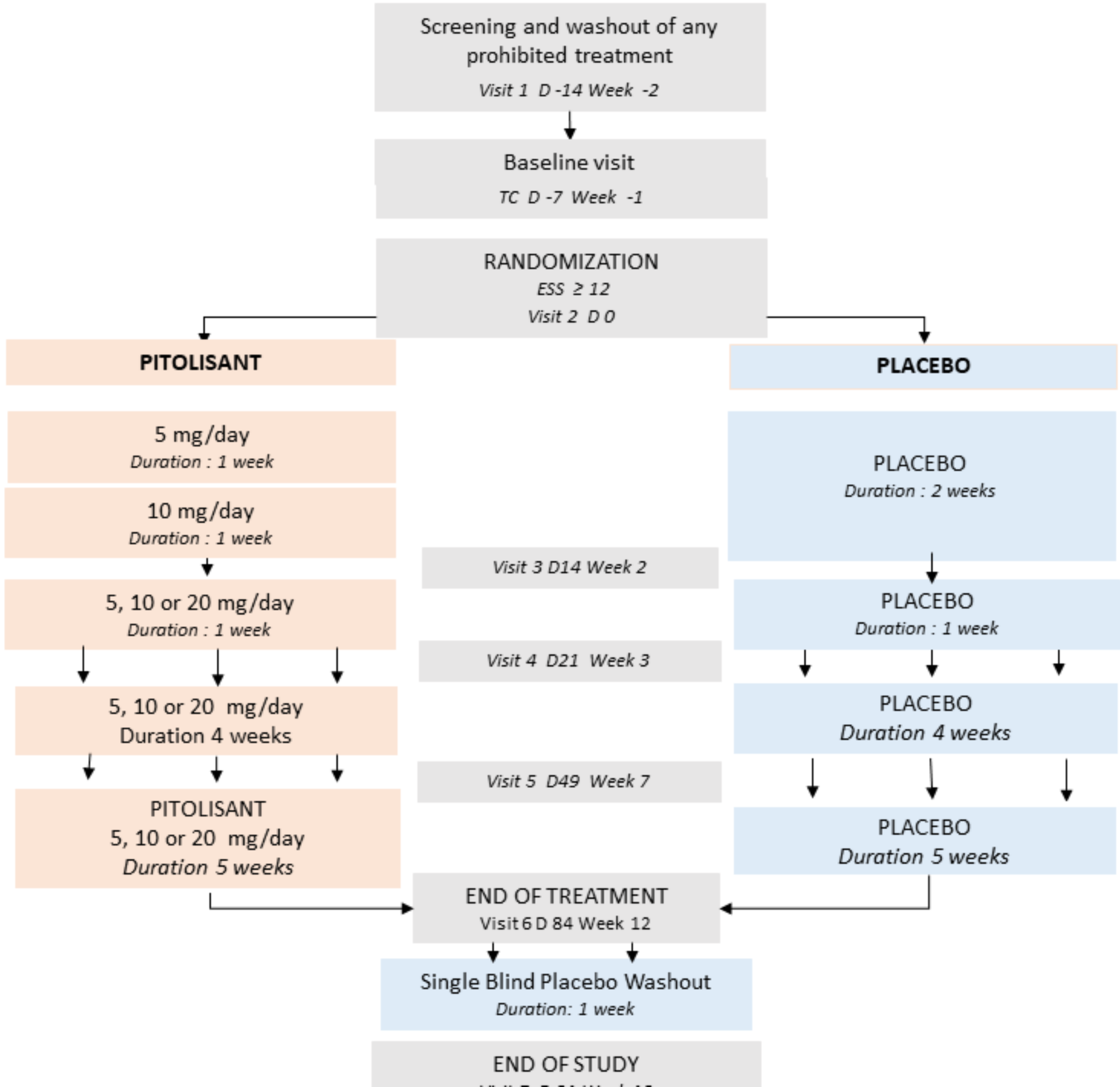
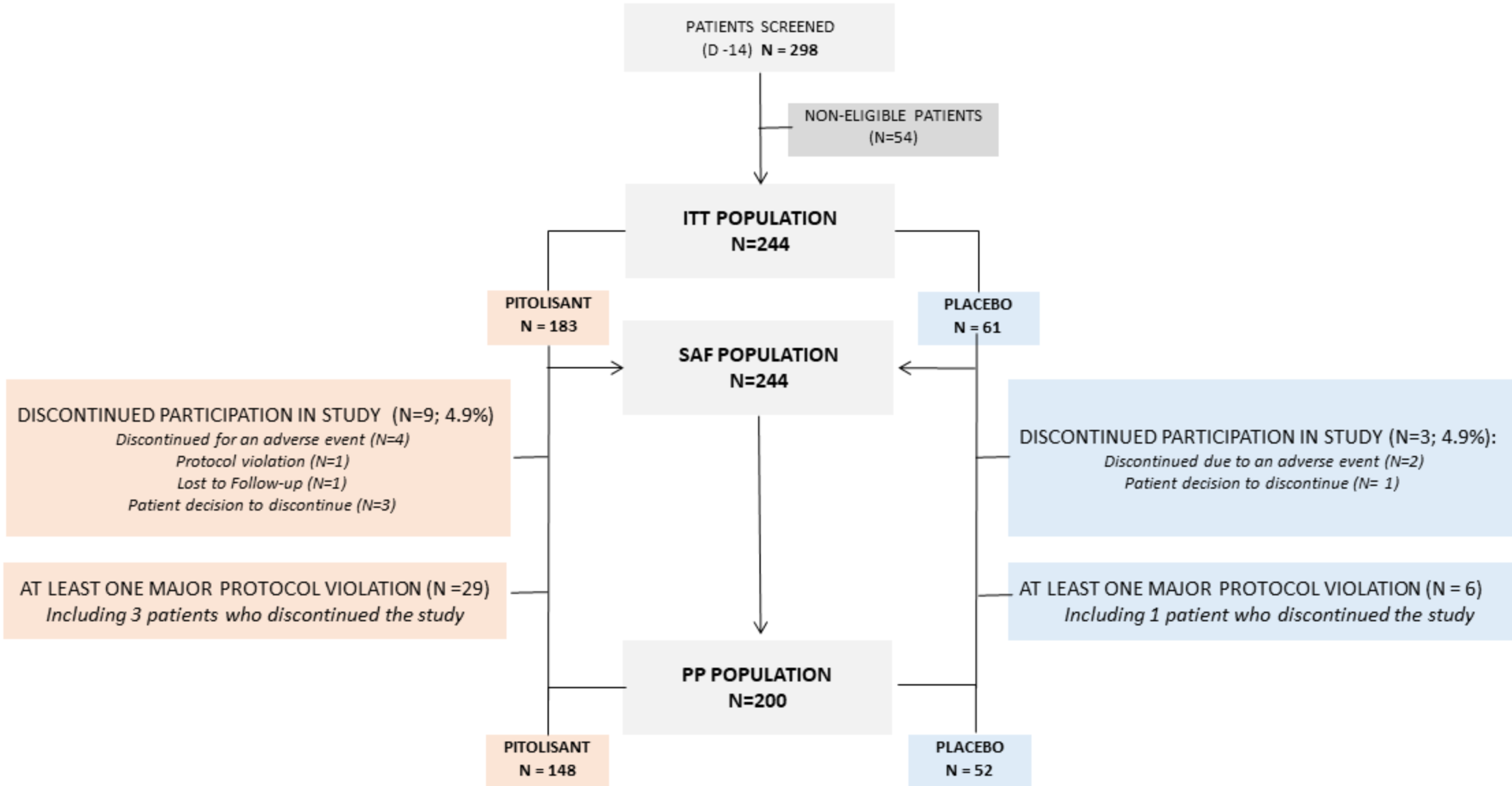
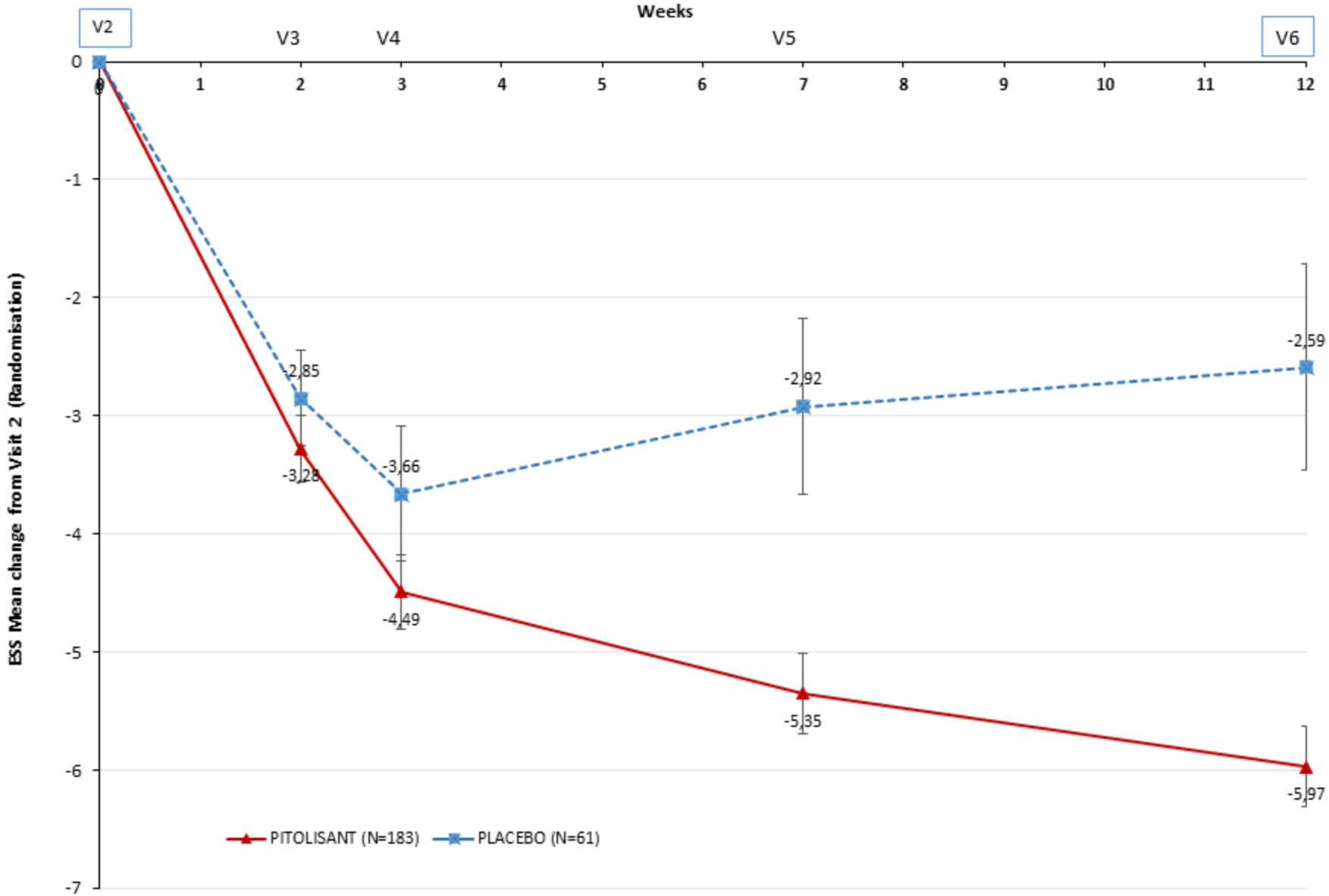
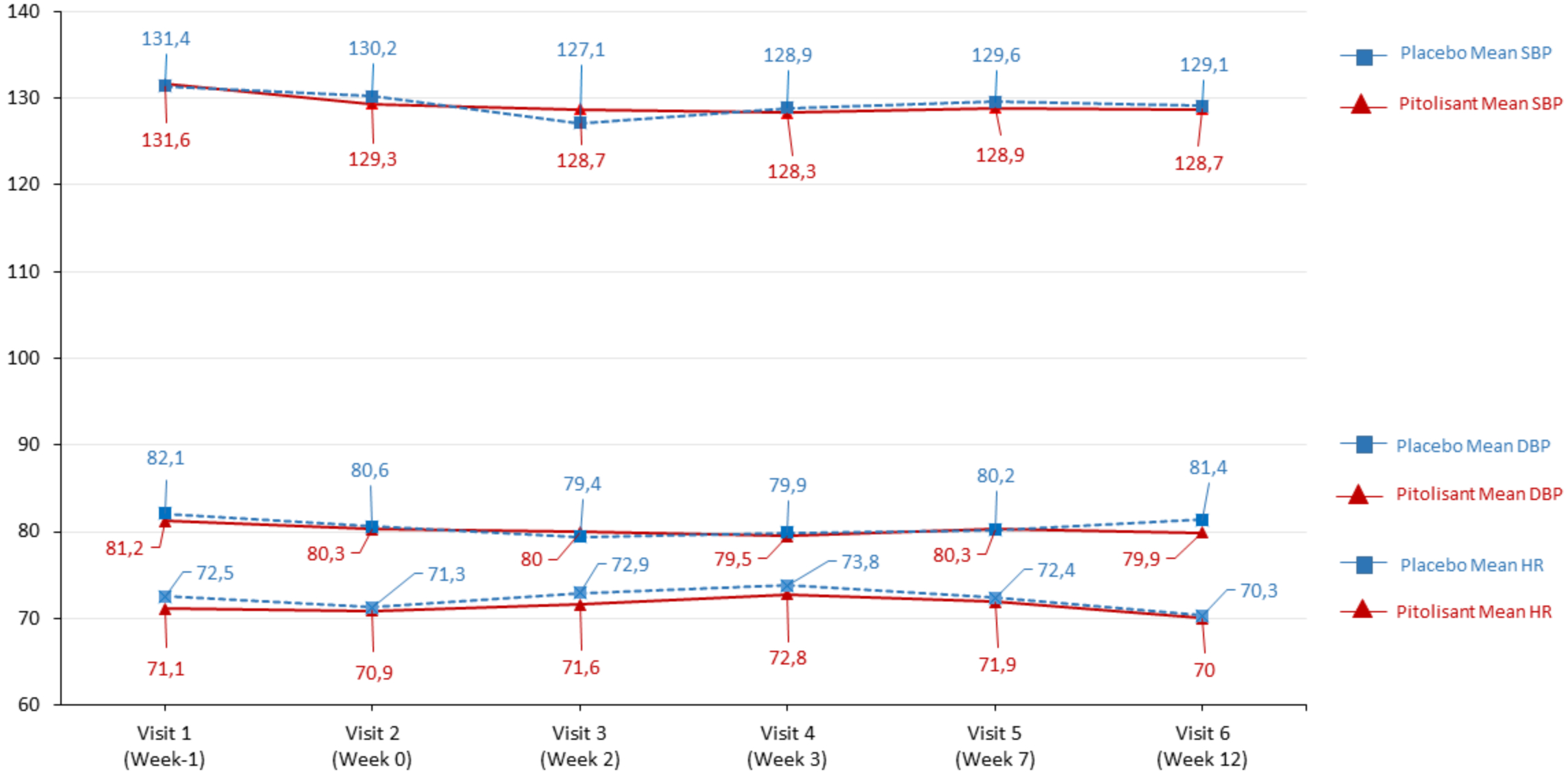


Figure 1: Study Design


PATIENTS SCREENED
(D -14) N = 298
NON-ELIGIBLE PATIENTS
(N=54)
ITT POPULATION
N=244
PITOLISANT
N = 183
PLACEBO
N = 61
SAF POPULATION
N=244
DISCONTINUED PARTICIPATION IN STUDY (N=9; 4.9%)
Discontinued for an adverse event (N=4)
Protocol violation (N=1)
Lost to Follow-up (N=1)
Patient decision to discontinue (N=3)
DISCONTINUED PARTICIPATION IN STUDY (N=3; 4.9%):
Discontinued due to an adverse event (N=2)
Patient decision to discontinue (N= 1)
AT LEAST ONE MAJOR PROTOCOL VIOLATION (N =29)
Including 3 patients who discontinued the study
AT LEAST ONE MAJOR PROTOCOL VIOLATION (N = 6)
Including 1 patient who discontinued the study
PP POPULATION
N=200
PITOLISANT
N = 148
PLACEBO
N = 52


Weeks
V2
V3
V4
V5
V6
0
1
2
3
4
5
6
7
8
9
10
11
12
-1
-2
-3
-4
-5
-6
-7
ESS Mean change from Visit 2 (Randomisation)
-2,85
-3,28
-3,66
-4,49
-2,92
-5,35
-2,59
-5,97
PITOLISANT (N=183)
PLACEBO (N=61)


140
130
120
110
100
90
80
70
60
131,4
130,2
127,1
128,9
129,6
129,1
131,6
129,3
128,7
128,3
128,9
128,7
82,1
80,6
79,4
79,9
80,2
81,4
81,2
80,3
80
79,5
80,3
79,9
72,5
71,3
72,9
73,8
72,4
70,3
71,1
70,9
71,6
72,8
71,9
70
Visit 1 (Week-1)
Visit 2 (Week 0)
Visit 3 (Week 2)
Visit 4 (Week 3)
Visit 5 (Week 7)
Visit 6 (Week 12)
Placebo Mean SBP
Pitolisant Mean SBP
Placebo Mean DBP
Pitolisant Mean DBP
Placebo Mean HR
Pitolisant Mean HR