20 May 2021
EMA/375687/2021
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Ozawade

International non-proprietary name: pitolisant

Procedure No. EMEA/H/C/005117/0000

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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Table of contents

List of abbreviations

AASM	American Academy of Sleep Medicine
ADHD	Attention Deficit/Hyperactivity Disorder
ADR	Adverse Drug Reaction
AE	Adverse Event
AFS	Awake Following Sleep
AHI	Apnea-hypopnea index
ALT/SGPT	Alanine aminotransferase
ASMF	Active substance master file
AST/SGOT	Aspartate aminotransferase
ANCOVA	Analysis of Covariance
APAP	Automatic positive airway pressure
AUC	Area under the concentration-time curve
BDI	Beck Depression Inventory
BFW	Behavior Following Wakening
BMI	Body Mass Index
BPAP	Bilevel positive airway pressure
CFU	Colony forming units
CGI	Clinical Global Improvement Scale
CHMP	Committee for Medicinal Products for Human use
CI	Confidence Interval
Cmax	Maximum observed concentration
CNS	Central nervous system
CPAP	Continuous Positive Airway Pressure
CUP	Compassionate Use Program
CVD	Cardiovascular disease
CYP450	Cytochrome P450
DB	Double-Blind
DSAR	Daytime Sleep Attack Rate
DSM-IV	Diagnostic System Medical, fourth version
DVS	Dynamic vapour sorption
ECG	Electrocardiogram
EC	European Commission
EDS	Excessive Daytime Sleepiness
EEG	Electro-Encephalogram
EMA	European Medicines Agency
EQ-5D	EuroQol Quality of Life Questionnaire
ESS	Epworth Sleepiness Scale
EU	European Union
GM	Geometric Mean
GC	Gas chromatography
GCMS	Gas chromatography mass spectrometry
GCP	Good Clinical Practices
GI	Gastrointestinal
GGT	Gamma-glutamyltranspeptidase
GTS	Getting to Sleep
HDPE	High density polyethylene
HPLC	High performance liquid chromatography
IC50	Half maximal inhibitory concentration
ICSD	International Classification of Sleep Disorders

ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
IR	Infrared
ITT	Intent to Treat
LCMS	liquid chromatography mass spectrometry
LED	Light-emitting diode
LoD	Limit of detection
LSEQ	Leeds Sleep Evaluation Questionnaire
MAA	Marketing Authorisation Application
MID	Minimum Clinically relevant Difference
MMSE	Mini Mental State Examination
MO	Major objection
M. Pt.	Melting point
MWT	Maintenance of Wakefulness Test
NDBA	*N*-Nitrosodibutylamine
NDEA	*N*-Nitrosodiethylamine
NI	Non-Inferiority
NMR	Nuclear magnetic resonance
NPIP	*N*-Nitrosopiperidine
OAD	Once a day
OCST	Out-of-centre sleep testing
OL	Open Label
OSA	Obstructive Sleep Apnoea Syndrome
OSleR	Oxford Sleep Resistance test
QoL	Quality of Life
PDE	Permitted daily exposure
PGOE	Patient's Global Opinion of the Effect
Ph. Eur.	European Pharmacopoeia
PK	Pharmacokinetic
PLM	Periodic Limbs Movement
ppb	parts per billion
PR	Prothrombin ratio
PSG	Polysomnography
QOS	Quality of Sleep
RCT	Randomised clinical trial
RERAs	Respiratory effort-related arousals
REM	Rapid Eye Movement
RH	Relative Humidity
SAE	Serious Adverse Event
SD	Standard Deviation
SDAD	Sleep Diary mean daily Alertness Duration
SDB	Sleep disordered breathing
SDDS	Sleep Diary mean daily Duration of Sleepiness episodes
SDNS	Sleep Diary mean daily Number of Sleep/Sleepiness episodes
SDWD	Sleep Diary mean Wakefulness Duration
SmPC	Summary of Product Characteristics
SOC	System Organ Class
TAMC	Total Aerobic Microbial Count
TEAE	Treatment-Emergent Adverse Event
TGA	Thermogravimetric analysis
Tmax	Time to reach maximum concentration
TMT	Trail Making Test
TTC	Threshold of toxicological concern
TYMC	Total Combined Yeasts/Moulds Count

UV	Ultraviolet
XRPD	X-ray powder diffraction

1. Background information on the procedure

1.1. Submission of the dossier

The applicant BIOPROJET PHARMA submitted on 8 November 2019 an application for marketing authorisation to the European Medicines Agency (EMA) for Ozawade, through the centralised procedure under Article 3 (a)of Regulation (EC) No 726/2004. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 26 July 2018.

The applicant applied for the following indication:

Ozawade is indicated in the treatment of Excessive Daytime Sleepiness (EDS) in patients with Obstructive Sleep Apnoea (OSA) and treated by Continuous Positive Airway Pressure (CPAP) but still complaining of EDS, or in patients with OSA refusing/not tolerating CPAP (see also section 5.1).

The legal basis for this application refers to:

Article 8.3 of Directive 2001/83/EC - complete and independent application

The application submitted is composed of administrative information, complete quality data, non-clinical and clinical data based on applicants' own tests and studies and/or bibliographic literature substituting/supporting certain test(s) or study(ies).

Information on Paediatric requirements

Pursuant to Article 7 of Regulation (EC) No 1901/2006, the application included an EMA Decision P/0188/2018 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP P/0188/2018 was not yet completed as some measures were deferred.

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

Additional Data exclusivity /Marketing protection

The applicant requested consideration of one year data exclusivity /marketing protection in regards of its application for a new indication of the orphan medicinal product Wakix in accordance with Article 14(11) of Regulation (EC) 726/2004.

The applicant requested consideration of one additional year marketing protection in regards of its application for a new indication in accordance with Article 14(11) of Regulation (EC) 726/2004, as Wakix and Ozawade belong to the same global marketing authorisation.

New active Substance status

The applicant requested the active substance pitolisant contained in the above medicinal product to be considered as a new active substance in comparison to pitolisant previously authorised in the European Union as Wakix.

Scientific advice

The applicant received the following Scientific advice on the development relevant for the indication subject to the present application:

Date	Reference	SAWP co-ordinators
20 September 2007	EMEA/H/SA/916/2/2007/SME/II	Cristina Sampaio, Fernando de Andrés Trelles
21 January 2010	EMEA/H/SA/916/2/FU/1/2009/SME/II	Thomas Lang, Beatriz Silva Lima

The initial Scientific Advice pertained to the following aspects:

- Excessive daytime sleepiness (EDS) is a debilitating symptom present in several diseases in which it may correspond to various aetiologies and respond differentially to various treatments. Therefore, the applicant had deliberately decided not to consider EDS as a single medical entity and selected to assess separately the utility of pitolisant, a drug belonging to a novel class of arousal-promoting agents, the inverse agonists of the histamine H3 receptor, in three distinct pathologies: Narcolepsy, Parkinson's Disease and Obstructive Sleep Apnoea (OSA).
- The agreement that although some instruments to assess EDS, commonly used in the three pathologies, i.e. the Epworth Scale and the Sleep Agenda, will be used in each of our clinical trials in these three pathologies, distinct additional instruments, distinct inclusion and efficacy criteria will also be used in these three cases. Data from each of these three pathologies could not, therefore, be extended to other pathologies.
- The acceptance of the indication Excessive daytime sleepiness (EDS), and the choice of assessing EDS separately in three distinct neurological pathologies.
- The acceptance of the escalating dose regimen adequate for the proposed Phase III studies, avoiding the usual dose-range finding study in parallel groups.
- The agreement on The Epworth Sleepiness Scale (ESS) score as the primary endpoint to measure the treatment effect on Excessive Daytime Sleepiness (EDS) in the three protocols: Narcolepsy, Parkinson's disease and Obstructive Sleep Apnoea.
- The agreement on the evaluation of diurnal sleep and sleepiness episodes will be recorded by the patients on the patient's diaries. This criterion will be used as the main secondary endpoint.
- The agreement on: a) in the three protocols, the secondary endpoint will be Maintenance Wakefulness Test (MWT), and nocturnal polysomnography or Osler. These measurements will be performed on a limited number of patients displaying an abnormal value at baseline, and in centres selected for their technical capacities to perform this test; b) on the number of patients proposed here below for EDS, based on the statistical hypothesis that the MID = 3, corresponding to an effect size = 0.5 in the main criteria for narcolepsy, OSA, and PD; C) that the duration of treatment detailed below is sufficient to document the safety/efficacy ratio of pitolisant.

The follow-up Scientific Advice pertained to the following aspects:

- The agreement that the total number already exposed, and planned number of patient proposed to be included in the Pivotal Phase III studies are sufficient to support a Marketing Authorisation in the relief of EDS in Parkinson Disease, i.e. 328 patients receiving pitolisant out of the 492 patients included in Phase III clinical trials for the evaluation of efficacy and that the total number already exposed and planned number of patient proposed to be included in the Pivotal Phase III studies are sufficient to support a Marketing Authorisation in the Relief of EDS in OSA.
- The agreement with the treatment dosage scheme, that will be individually adapted to each patient, and that the EMEA consider as necessary to assess PK profiles on special populations of healthy human volunteers e.g. elderly persons, persons with impaired renal or hepatic functions; the need to add a clinical drug-drug interaction studies considering the polytherapy encountered in the elderly.

1.2. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Johann Lodewijk Hillege Co-Rapporteur: Bruno Sepodes

The appointed co-rapporteur had no such prominent role in Scientific advice relevant for the indication subject to the present application.

The application was received by the EMA on	8 November 2019
The procedure started on	27 February 2020
The Rapporteur's first Assessment Report was circulated to all CHMP members on	18 May 2020
The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on	20 May 2020
The PRAC Rapporteur's first Assessment Report was circulated to all PRAC members on	2 June 2020
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	N/A
The PRAC Rapporteur's updated Assessment Report was circulated to all PRAC members on	11 June 2020
The CHMP agreed on the consolidated List of Questions to be sent to the applicant during the meeting on	25 June 2020
The applicant requested a clock-stop extension to submit the responses to the CHMP consolidated List of Questions on	26 August 2020
The applicant submitted the responses to the CHMP consolidated List of Questions on	9 October 2020
The Rapporteurs circulated the Joint Assessment Report on the responses to the List of Questions to all CHMP members on	18 November 2020

The PRAC Rapporteur's updated Assessment Report was circulated to all PRAC members on	26 November 2020
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	26 November 2020
The Rapporteurs circulated the updated Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP members on	9 December 2020
The CHMP agreed on a list of outstanding issues to be sent to the applicant on	10 December 2020
The applicant requested a clock-stop extension to submit the responses to the CHMP List of Outstanding Issues on	28 January 2021
The applicant submitted the responses to the CHMP List of Outstanding Issues on	25 February 2021
The Rapporteurs circulated the Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP members on	11 March 2021
The Rapporteurs circulated the updated Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP members on	18 March 2021
The CHMP agreed on a 2nd list of outstanding issues to be sent to the applicant on	25 March 2021
The applicant submitted the responses to the CHMP 2nd List of Outstanding Issues on	31 March 2021
The Rapporteurs circulated the Joint Assessment Report on the responses to the 2nd List of Outstanding Issues to all CHMP members on	9 April 2021
The Rapporteurs circulated updated the Joint Assessment Report on the responses to the 2nd List of Outstanding Issues to all CHMP members on	15 April 2021
The CHMP agreed on a 3rd list of outstanding issues to be sent to the applicant on	22 April 2021
The applicant submitted the responses to the CHMP 3rd List of Outstanding Issues on	27 April 2021
The Rapporteurs circulated the Joint Assessment Report on the responses to the 3rd List of Outstanding Issues to all CHMP members on	14 May 2021
The CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a marketing authorisation to Ozawade on	20 May 2021

2. Scientific discussion

2.1. Problem statement

2.1.1. Disease or condition

Obstructive sleep apnoea (OSA) is a condition of worldwide major health concern which has multi-organ consequences and results in considerable economic, health care and social burden (Levy et al. 2015, Mc Nicolas et al. 2018).

Excessive daytime sleepiness (EDS), and fatigue are among the chief complaints in patients with OSA, and have disabling consequences: impaired attention and vigilance, cognitive dysfunction, loss of productivity at work, deterioration in quality-of-life, and increased risk of occupational and motor vehicle accidents (Rosenzweig et al. 2015, Bucks et al. 2017).

2.1.2. Epidemiology

OSA afflicts around 2-4% of the adult population (2-4% in males and 1-2% in females of average age (Mc Nicolas 2008, Young et al. 2002, Maspero et al. 2015).

2.1.3. Biologic features

The proposed mechanism for EDS in OSA patients is sleep disturbance and loss of sleep resulting from microarousals produced by increased ventilatory effort (Nieto et al. 2000; Peppard et al. 2000).

2.1.4. Clinical presentation, diagnosis

Diagnostic criteria for an obstructive sleep apnea syndrome (OSAS) were established by the Report of an American Academy of Sleep Medicine Task Force published in 1999 (Flemons et al. 1999), and often referred to as the "Chicago criteria": OSA syndrome requires the presence of sleep-disordered breathing (SDB) measured in an overnight sleep study by one of the two accepted methods of objective testing: in-laboratory polysomnography (PSG) or home testing with portable monitors (PM).

It should be combined with the presence of symptoms typical of the disorder, most notably excessive daytime sleepiness (EDS). Furthermore, different severity levels were identified according to the apnea-hypopnea frequency per hour (AHI) with an AHI >5 being required for significant SDB, an AHI between 5 and 15 representing mild, between 15 and 30 representing moderate, and AHI >30 representing a severe disorder when relevant clinical symptoms are also present.

2.1.5. Management

Continuous positive airway pressure (CPAP) is the treatment of choice for most patients with OSA (Loube et al. 1999, Kushida et al. 2006, Kushida et al. 2008). CPAP aims to stabilise the upper airway with a constant flow of air, preventing the collapse of the airway during sleep. When used properly, CPAP reduces apnoea and hypopnea rate, often normalises arterial blood oxygen saturation, decreases sleep fragmentation, and improves sleep quality. As a result, alertness, mood, cognitive function, and quality of life improve (Batool-Anwar et al. 2016, Patil et al. 2019a). Furthermore, CPAP reduces risks of cardiovascular events in obstructive sleep apnoea patients.

The limitations of CPAP treatment lie mainly in acceptance and adherence. Like all chronic therapies, compliance with CPAP (use > 3hours per night) is difficult to maintain over time, and CPAP adherence is reported only for up to 50% of subjects with OSA (Hussain et al. 2014). Failure to adhere to CPAP therapy may occur in 25–50% of patients, with patients typically abandoning therapy within the first 4 weeks of treatment (Queiroz et al. 2014) and 12% to 25% may discontinue CPAP within 3 years (Akram Khan, 2008).

In a long term study of the use of CPAP in 137 sleep apnoea patients followed during 9 years, Bizieux-Thaminy et al. outlined that among 30 patients out of 137 (22%) who stopped CPAP, 10% of them stopped CPAP within the 6 first months, 30% within the year, and 67% within 3 years (Bizieux-Thaminy et al. 2005). The most common problems reported with CPAP were nasal stuffiness, sensation of cold air, noise and mask pressure (Douglas & Engleman 1998).

Moreover, in some patients compliant to CPAP, despite the improvement of respiratory disturbance during sleep, EDS (and fatigue) may persist. This is known as residual excessive sleepiness (RES) (Guilleminault et al. 1996, Englemann et al. 1998, Santamaria et al. 2007, Pack et al. 2001). It is estimated that 6 % of compliant CPAP treated OSA patients (since 1 year) experience RES when comorbid sleep pathologies (such RLS or narcolepsy) have been ruled out (Pepin et al. 2009). The explanation for this condition is based on the hypothesis that chronic hypoxia may cause irreversible neuronal injury, dopamine dysfunctions, increased oxidative stress, and even apoptosis and gliosis would explain the absence of improvement in sleepiness experienced by some patients. These patients, who often complain of an important EDS and fatigue which represent a serious embarrassment in their everyday life, also claim a symptomatic treatment. In these cases, pharmacotherapy could be used as an adjunct to CPAP for treatment of residual excessive sleepiness.

In view of compliance issues for CPAP, or residual excessive sleepiness despite CPAP treatment, alternative modalities such as pharmacologic symptomatic treatment may be of great interest to treat persistent residual excessive daytime sleepiness and fatigue, which lead to a decreased quality of life and a risk in car driving or performance of professional or daily life operations.

As of January 2020, Sunosi (solriamfetol, EMEA/H/C/004893/0000) is the only approved pharmacological treatment of EDS in OSA in Europe. It is indicated for patients with OSA whose EDS has not been satisfactorily treated by primary OSA therapy, such as continuous positive airway pressure (CPAP).

About the product

Pitolisant is a histamine H3-receptor antagonist/inverse agonist which, via its blockade of histamine auto-receptors enhances the activity of brain histaminergic neurons, a major arousal system with widespread projections to the whole brain. It has been previously authorised in the European Union as Wakix for the treatment of narcolepsy.

Type of Application and aspects on development

This application for marketing authorisation to the European Medicines Agency (EMA) was submitted under Article 3 (a)of Regulation (EC) No 726/2004.

2.2. Quality aspects

2.2.1. Introduction

The finished product is presented as film-coated tablets containing pitolisant hydrochloride, equivalent to 4.45 or 17.8 mg of pitolisant, respectively.

Other ingredients are:

Tablet core: microcrystalline cellulose (E 460), crospovidone type A (E 1202), talc (E 553b), magnesium stearate and colloidal anhydrous silica (E 551);

Film-coating: poly(vinyl alcohol) (E1203), titanium dioxide (E 171), macrogol 3350(E 1521) and talc (E 553b).

The product is available in HDPE bottles with a tamper-evident, child-resistant, polypropylene screw caps fitted with desiccant (silica gel) as described in section 6.5 of the SmPC.

2.2.2. Active Substance

General information

The chemical name of pitolisant hydrochloride is 1-{3-[3-(4-chlorophenyl)propoxy]propyl}piperidine corresponding to the molecular formula $C_{17}H_{26}ClNO.HCl$. It has a relative molecular mass of 332 g/mol and the following structure:

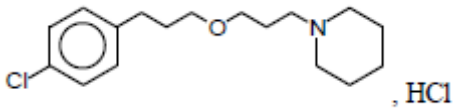


Figure 1: Active substance structure

The chemical structure of pitolisant hydrochloride was elucidated by a combination of IR spectrophotometry, mass spectrometry, NMR spectroscopy, elemental analysis, UV spectrophotometry and single crystal x-ray diffraction. The solid-state properties of the active substance were measured by x-ray powder diffraction (XRPD), thermogravimetric analysis (TGA), dynamic vapour sorption (DVS) and a polymorphism study.

The active substance is a white or almost white, crystalline powder which is hygroscopic above 75% RH. It is very soluble in aqueous media across the physiological pH range. Only one stable polymorphic form has been identified which is routinely produced by the commercial manufacturing process. Pitolisant is achiral.

Manufacture, characterisation and process controls

Detailed information on the manufacturing of the active substance has been provided in the restricted part of the ASMF and it was considered satisfactory. Two manufacturers are involved on the process – one manufactures an intermediate and the other is responsible for all other steps.

Pitolisant hydrochloride is synthesized in 3 main steps followed by a salt formation using well-defined starting materials with acceptable specifications.

The manufacturing process is straightforward, using well-known reactions and is described in sufficient detail. The characterisation of the active substance and its impurities are in accordance with the EU guideline on chemistry of active substances. Potential and actual impurities, including potentially mutagenic impurities were well discussed with regards to their origin and characterised. The control strategy to ensure the quality of the active substance consists of process control and specifications on raw materials, intermediates and the active substance and has been justified by a series of impurity spike and purge studies. Isopropyl methanesulfonate is a potentially genotoxic impurity formed in the final step due to the presence of isopropyl alcohol and is controlled in the active substance specification. Adequate in-process controls are applied during the synthesis. The specifications and control methods for intermediate products, starting materials and reagents have been presented.

The quality of the active substance used in the various phases of the development is considered to be comparable with that produced by the proposed commercial process.

Pitolisant hydrochloride is stored in double food-grade low density polyethylene bags (internal bags) closed by a tamper-evident plastic tie, overwrapped in a foil liner (external bags) hermetically sealed and placed in a fibreboard drum. The primary contact materials which comply with the EC directive 2002/72/EC and EC 10/2011 as amended.

Specification

The active substance specification includes tests for appearance, identity (IR, HPLC, M. Pt.), identity of chloride (Ph. Eur.), clarity and colour of solution (Ph. Eur.), water content (Ph. Eur.), residue on ignition (Ph. Eur.), related substances (HPLC), isopropyl methanesulfonate (GCMS), residual solvents (GC), assay (HPLC) and particle size distribution (laser diffraction).

Limits for impurities are set according to ICH Q3A and ICH M7.

The analytical methods used have been adequately described and non-compendial methods appropriately validated in accordance with the ICH guidelines. Satisfactory information regarding the reference standards used for assay and impurities testing has been presented.

Batch analysis data from 17 pilot to production scale batches of the active substance are provided. The results are within the specifications and consistent from batch to batch.

Stability

Stability data from 6 production scale batches of active substance from the proposed manufacturers, stored in the intended commercial package for up to 60 months under long term conditions (25°C / 60% RH) and for up to 6 months under accelerated conditions (40°C / 75% RH) according to the ICH guidelines were provided. Samples were tested for appearance, water content, impurities and assay. The analytical methods used were the same as for release.

Pitolisant hydrochloride is very stable under long term and accelerated conditions.

Forced degradation studies including exposure to neutral aqueous, acid, basic and oxidative conditions, heating and high intensity UV light (solid and solution), were conducted to investigate the stability indicating nature of the analytical methods for impurities and assay. However, pitolisant is very stable and thus, the standard stressed conditions employed did not lead to enough degradation to draw a firm conclusion. Therefore, the CHMP recommended to conduct further forced degradation studies using harsher conditions and to provide the results by June 2021. All tested parameters were within the specifications under all storage conditions and no trends were observed.

Photostability testing following the ICH guideline Q1B was performed on one batch. Pitolisant hydrochloride is not photosensitive.

The stability results indicate that the active substance manufactured by the proposed suppliers is sufficiently stable. The stability results justify the proposed retest period of 60 months in the proposed container between 15°C and 25°C, with limited excursions permissible up to 30°C.

2.2.3. Finished Medicinal Product

Description of the product and Pharmaceutical development

The finished product is presented as film-coated tablets containing either 5 or 20 mg of pitolisant hydrochloride, equivalent to 4.45 mg or 17.8 mg of pitolisant free base (rounded to 4.5 and 18 mg in the SmPC). The 4.5 mg tablets are white, round and biconvex with a diameter of approximately 3.7 mm engraved with "5" on one side. The 18 mg tablets are white, round and biconvex with a diameter of approximately 7.5 mm engraved with "20" on one side. Both strengths of tablet contain the same qualitative and quantitative composition of excipients.

The aim of pharmaceutical development was an immediate release oral solid dosage form. The formulation development took into account relevant physicochemical properties of the active substance: a fine crystalline powder with good compressibility properties and satisfactory density which is not hygroscopic until 75 % RH, is very soluble in water until pH 7.5, is sensitive to excessive oxidative conditions and has a very strong and prolonged bitter taste. The other chosen excipients are used in standard amounts for a solid oral dosage form. Compatibility of the active substance with the chosen excipients was demonstrated on studies with binary and ternary mixtures. All excipients are well known pharmaceutical ingredients and their quality is compliant with Ph. Eur standards. There are no novel excipients used in the finished product formulation. The list of excipients is included in section 6.1 of the SmPC and in paragraph 2.2.1 of this report.

Different formulations were developed and used throughout clinical development. A capsule was used in phase I studies. In phase II, 18 mg uncoated tablets were used, which had the same composition as the final core tablets but bearing a score line to allow dose titration. From phase III onwards, coated tablets, with the same composition as the proposed commercial formulation and a second lower tablet strength was introduced. The coating was added in order to mask the bitter taste of the active substance. In some cases, over-encapsulation was applied for blinding purposes in clinical trials. The applicant provided sufficient data to show that all these different formulations (capsules, coated, uncoated and over-encapsulated tablets) have similar dissolution profiles and are bioequivalent. The information provided about clinical formulations is adequate.

The dissolution method was developed, bearing in mind the high aqueous solubility of the active substance across the physiological pH range. The medium (0.1 M HCl), the apparatus (paddle with sinker) and paddle speed (50 rpm) were all chosen as they provided the most discriminatory medium. Different volumes are used to account for the different strengths: 1000 ml for the 18 mg tablets and 500 ml for the 4.5 mg tablets. Discriminatory power was investigated by comparing the dissolution profiles of mis-manufactured batches. For the 18 mg tablet, this consisted of a dry-granulated batch (by double compression), an over-lubricated batch and an over-compressed batch. For the 4.5 mg tablet, this consisted of an over-compressed batch and a batch over-encapsulated in a hard gelatine capsule. Considering the high solubility of the active substance, the dissolution method is considered to be suitably discriminatory when a limit of Q=80% after 15 mins is applied.

The principle of the tablet manufacturing process has remained consistent since it was introduced into phase II clinical trials. The tablet is made by blending and direct compression to avoid exposing the active substance to high humidity. Operating parameters for the different unit operations (blending, lubrication, compression and film-coating) were optimised during development of the 18 mg tablet and suitable controls have been set. The parameter settings were then adapted for the 4.5 mg tablet.

The primary packaging is an HDPE bottle with a tamper evident, child-resistant polypropylene screw cap fitted with a desiccant. The materials comply with Ph. Eur. and EC requirements. The choice of the container closure system has been validated by stability data and is adequate for the intended use of the product.

Manufacture of the product and process controls

The manufacturing process consists of 6 main steps: blending 1, blending 2 (including lubrication), compression, preparation of film-coating suspension, film-coating and packaging. The process is considered to be a standard manufacturing process. Each strength of tablet is manufactured at a different site with a different batch size.

The manufacturing process have been validated on 3 production scale batches of each strength. It has been demonstrated that the manufacturing process is capable of producing the finished product of intended quality in a reproducible manner. The in-process controls are adequate for this type of manufacturing process and pharmaceutical form.

Product specification

The finished product release and shelf-life specifications for the 4.5 mg tablets include appropriate tests for this kind of dosage form including description (visual), identification (HPLC, UV), identification of titanium dioxide (Ph. Eur.), uniformity of mass (Ph. Eur.), uniformity of dosage units (Ph. Eur.), water content (Ph. Eur.), disintegration time (Ph. Eur.), dissolution (HPLC), assay (HPLC), impurities (GC, HPLC) and microbiological quality (Ph. Eur.). The specifications for the 18 mg tablets are identical, except for the assay test given the different active substance content, and for appearance, given the different tablet sizes.

Limits for degradation products are set below the qualification threshold as per ICH Q3B. The limit for the dissolution test is considered sufficiently tight.

The potential presence of elemental impurities in the finished product has been assessed following a risk-based approach in line with the ICH Q3D Guideline for Elemental Impurities. Batch analysis data on 9 batches using a validated analytical method was provided, demonstrating that each relevant elemental impurity was not detected above 30% of the respective PDE. Based on the risk assessment and the presented batch data, it can be concluded that it is not necessary to include any elemental impurity controls in the finished product specification. The information on the control of elemental impurities is satisfactory.

A risk evaluation concerning the presence of nitrosamine impurities in the finished product was submitted at the request of CHMP as a major objection (MO). The applicant considered all suspected and actual root causes in line with the "Questions and answers for marketing authorisation holders/applicants on the CHMP Opinion for the Article 5(3) of Regulation (EC) No 726/2004 referral on nitrosamine impurities in human medicinal products" (EMA/409815/2020) and the "Assessment report-Procedure under Article 5(3) of Regulation EC (No) 726/2004- Nitrosamine impurities in human medicinal products" (EMA/369136/2020). The active substance and its precursor both contain tertiary amines which could potentially react to form nitrosamines (e.g. *N*-nitrosopiperidine, NPIP) in the

presence of nitrite. In addition, triethylamine and tetrabutylammonium bisulfate are reagents in the process which are known precursors to NDEA and NDBA. However, there are no intentionally added nitrosating agents and thus, there is no significant risk of nitrosamine contamination. Nonetheless, the applicant opted to screen 3 batches of each strength of finished product for an array of common nitrosamines (including NPIP, NDEA and NDBA) using validated and suitably sensitive LCMS and GCMS methods. No nitrosamines were observed above the limit of detection (LoD, 5 ppb). Therefore, no additional control measures are deemed necessary.

The analytical methods used for release and shelf-life testing have been adequately described and appropriately validated in accordance with the ICH guidelines. Satisfactory information regarding the reference standards used for assay and impurities testing has been presented.

Batch analysis results are provided for 3 production scale batches of each strength, along with batches of the 18 mg tablets and capsules produce throughout development, confirming the consistency of the manufacturing process and its ability to manufacture to the intended product specification.

The finished product is released on the market based on the above release specifications, through traditional final product release testing.

Stability of the product

Stability data from 6 production scale batches of both strengths of finished product stored for up to 36 months under long term conditions (25°C / 60% RH), up to 36 months under intermediate conditions (30°C / 75% RH), and for up to 6 months under accelerated conditions (40°C / 75% RH) according to the ICH guidelines were provided. The batches of medicinal product are identical to those proposed for marketing and were packed in the primary packaging proposed for marketing. Additional stability data was provided on 6 batches of tablets used in clinical studies, including cross-scored tablets stored in slightly different but representative packaging.

Samples were tested according to the release specifications with the omission of titanium dioxide identity and uniformity of mass. The analytical procedures used are stability indicating. No significant trends were observed for any of the measured parameters and all remained within specification under each condition.

In addition, 2 batches of the 18 mg strength were exposed to light as defined in the ICH Guideline on Photostability Testing of New Drug Substances and Products. The finished product is not photosensitive.

Forced degradation studies were performed on two batches of the 18 mg tablet. The finished product was exposed to heat (for one week at 70°C), acid conditions (HCl 1M for 48 hours at room temperature), basic conditions (NaOH 1M for 48 hours at room temperature), and oxidative conditions (H_2O_2 l for 48 hours at room temperature). The finished product is very stable though less so than the active substance alone. Degradation was observed only under extreme oxidising conditions and to a lesser extent, acidic aqueous conditions.

In-use stability studies simulating up to 40 days of use in the HDPE bottle were performed on samples of both strengths starting after different storage time points under long term, intermediate and accelerated conditions. No trends were observed and all tested parameters remained within specification. Therefore, no specific storage condition or shelf life is required after the first opening of the bottles.

Based on available stability data, the proposed shelf-life of 36 months without special storage conditions as stated in the SmPC (section 6.3) is acceptable.

Adventitious agents

No excipients derived from animal or human origin have been used.

2.2.4. Discussion on chemical, pharmaceutical and biological aspects

Information on development, manufacture and control of the active substance and finished product has been presented in a satisfactory manner. The results of tests carried out indicate consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in clinical use. The major objection relating to the potential presence of nitrosamine impurities was resolved by a combination of risk assessment and confirmatory testing.

At the time of the CHMP opinion, there was one minor unresolved quality issue relating to the stability-indicating nature of the active substance impurities and assay methods which has no impact on the benefit/risk ratio of the product. The CHMP recommended further forced degradation studies to address this issue.

2.2.5. Conclusions on the chemical, pharmaceutical and biological aspects

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SmPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way.

2.2.6. Recommendation for future quality development

In the context of the obligation of the MAHs to take due account of technical and scientific progress, the CHMP recommends the following points for investigation:

- The applicant should conduct further forced degradation studies on the active substance release methods using harsher conditions and provide the results by June 2021 to re-confirm their stability-indicating nature.

2.3. Non-clinical aspects

2.3.1. Introduction

The Applicant presented results of a full non-clinical programme. Most of the non-clinical studies have been previously assessed and described in the context of Marketing Authorisation Application for Wakix.

2.3.2. Pharmacology

The non-clinical pharmacology programme for pitolisant consisted of *in vitro* assays and *in vivo* pharmacodynamic studies.

Primary pharmacodynamic studies

Pitolisant binds human histamine 3 receptor (H3R) with Ki values ranging from 1.0 to 2.4 nM (corresponding to IC_{50} values of 3.8-5.2 nM). Significant inter-species variation in the affinity for the

H3R was observed since pitolisant binds mouse, rat and monkey H3R with Ki values reaching 5.7-14 nM, 7.3 nM and 1.6 nM, respectively. This was attributed to a small difference in receptor sequences between species. In functional assays, pitolisant behaved as an antagonist/inverse agonist at the H3R, notably in one study showing a concentration-dependent decrease in the coupling to human H3R to G-protein with an EC_{50} and Emax values reaching 1.5 nM and 25%, respectively.

Pitolisant was not specific for H3R over sigma σ1 and σ2 receptors. Pitolisant binds to human sigma-1 receptor with a subnanomolar Ki (Ki = 0.5 nM). It showed a functional activity on sigma-1 receptor-mediated calcium flux, demonstrating agonism with an EC_{50} of 402 nM. In vivo, it showed an antidepressant effect in the mouse tail suspension test at a dose of 10 mg/kg, i.p. Regarding sigma-2 receptors, no in-vivo functional tests are available, but the in vitro test showed that pitolisant binds to sigma-2 receptors with a Ki of 6.5 nM and an IC_{50} of 8.55 nM. In a sigma-2 receptor-mediated calcium flux functional assay, pitolisant did not elicit agonist activity but behaved as an antagonist as it decreased haloperidol-induced calcium release with an IC_{50} of 10 µM.

In vivo studies showed that pitolisant enhanced the activity of histaminergic neurons as shown by the increase in brain levels of t-MeHA with oral ED_{50} values reaching 1.6-2.6 mg/kg in mice and 3 mg/kg in rats. In mice treated subchronically, the effect was similar and no tachyphylaxis was observed. In other microdialysis experiments, pitolisant (10 mg/kg, i.p.) activated dopaminergic, noradrenergic, and cholinergic neuronal projections to the prefrontal cortex as well as histaminergic projections to the hippocampus in rats. However, pitolisant was devoid of any effect on the dopamine release in the nucleus accumbens (in contrast to modafinil). In line with these results, pitolisant (10 mg/kg, p.o.) increased the turnover of dopamine in the prefrontal cortex, as well as the turnover of noradrenaline in hypothalamus, hippocampus and cortex of mice.

To support the use of pitolisant in narcoleptic patients, its effects on the sleep/wake cycle and on EEG pattern were investigated in healthy mice and cats, as well as in a mouse model of narcolepsy (orexin KO mouse). It was shown that it increased the duration of waking at the expense of SWS and PS with corroborating EEG changes at oral doses ≥10 mg/kg. In orexin KO mice, the results also suggested that pitolisant may have an anti-cataplectic effect.

In MPTP-treated cats, a model of Parkinson's disease, pitolisant exerted a wake-promoting effect. In this model, the motor and sleep-wake disorders could be reversed partially by the administration of current dopaminergic anti-PD compounds such as L-DOPA or ropinirole. Both compounds improved the MPTP-induced SWS hypersomnia and tended to suppress the increase in REM sleep, with such effects differing slightly according to the delay after MPTP treatment. Their wake-enhancing effect was, however, less potent than that seen with pitolisant at the oral dose of 10 mg/kg.

No additional primary pharmacology studies were performed to support the use of pitolisant in treatment of excessive daytime sleepiness in patients suffering from OSA, with or without CPAP. The rationale for its use is solely based on pitolisant's properties to increase wakefulness, which may counteract excessive daytime sleepiness.

Secondary pharmacodynamic studies

Pitolisant (15 mg/kg, i.p.) reversed scopolamine-induced learning deficit and the natural forgetting in mice. These pro-cognitive effects are hypothesised to be related to treatment-related direct arousing effect and/or increase in brain acetylcholine.

The effects of pitolisant on different types of seizures were investigated in rodents. The results suggested that it has anti-epileptic effect on absence seizures (rat model, 20 mg/kg, p.o.), and on temporal lobe seizures (kainate mice) at 10 mg/kg, p.o. In the latter model, results at 20 mg/kg, p.o. suggested, however, that it may trigger generalised clonic seizures in epileptic subjects. In addition, pitolisant was not active on generalised tonic-clonic seizures in mice (20 mg/kg, p.o.).

In mice, pitolisant attenuated the hyperlocomotion induced by moderate doses of methamphetamine and by MK-801 (dizocilpine), reduced the apomorphine-induced disruption of the pre-pulse inhibition (84 dB), and normalised the cognitive performance of dopamine transporter KO mice (no significant effect in wild-type mice). These experiments suggest that pitolisant may modulate dopaminergic and glutamatergic transmissions.

Human metabolites of pitolisant (BP2.951, BP1.8054, BP1.9733, BP1.3484, BP1.3473, BP1.8186, BP1.10749 and BP1.10556) were shown not to cross the blood-brain barrier or to be present at very low levels. In addition, all these metabolites were found inactive in the µmolar range on a large set of ~170-180 receptors, channels and transporters.

Safety pharmacology programme

Safety pharmacology studies showed that pitolisant has the ability to prolong the QT interval in humans. In vitro, it blocked hERG currents with an IC50 of 1.3 µM and affected action potential parameters in rabbit Purkinje fibres with effects suggesting that it blocks sodium, calcium and potassium channels at concentrations higher than 1 µM.

In vitro data on major human metabolites show no significant hERG channel blocking activity at concentrations up to 17 µM for BP2.951 (phase I metabolite) and Ki values of other human metabolites of pitolisant (BP2.928, BP1.8054, BP1.9733, BP1.3473, BP1.3484, BP1.8186, BP1.10556 and BP1.10749) in the [^{3}H]-dofetilide binding assay on membranes from HEK-293 cells stably expressing hERG were found to be of 4.2 µM (BP2.928) and higher than 10 µM (BP1.8054, BP1.9733, BP1.3473, BP1.3484, BP1.10556 and BP1.10749).

In anaesthetised rabbits, pitolisant was without any effect on the QTc interval. In telemetered dogs, a first study using the oral route did not show any adverse effect, but the systemic exposure to pitolisant was low, and therefore additional studies were performed using the intravenous route. At 1.5 mg/kg, i.v., the QTc intervals (QTcF and QTcV) were prolonged slightly (+10%) but significantly up to 6 hours post-dosing when compared to pre-dose values, but not when compared to the vehicle control group. However, the effect in pitolisant-treated animals was more long-lasting, and the values of the QTc interval observed following the administration of pitolisant were overall slightly higher than those observed following the vehicle administration. Therefore, a slight effect on QTc (prolongation) interval could not be excluded in this study. In the second intravenous telemetered dog study, a 3-fold higher dose caused rapid shortenings of PR, QTcF, and QTcV intervals which occurred together with rapid and marked increases in blood pressure and heart rate.

The effect of pitolisant on respiratory parameters was investigated in pentobarbital-anaesthetised rats treated i.v. at 0.5, 1, 2, 4, and 6 mg/kg. No adverse effect on measured parameters was noted at up to 4 mg/kg. At 6 mg/kg, a clear increase of the tidal volume was noted.

The Irwin test showed signs of central excitation from the low dose level (3 mg/kg, p.o.), with additional findings of muscular hypotony and sedation, and changes in state of mood at 30 mg/kg and above. Trace of tremors was observed at 60 mg/kg and minimal appearance of opisthotonus and few tonic and clonic convulsions at 100 mg/kg. Furthermore, pitolisant was shown to display a pro-convulsant activity at doses higher than 30 mg/kg, p.o. in the pentylenetetrazole-induced convulsion mouse model. Overall, pitolisant induced a dose-dependent increase in central excitation leading to the appearance of convulsions.

No treatment-related effect on barbital-induced sleep was shown in rats at up to 60 mg/kg, p.o. however this result should be interpreted with caution since the oral route of administration used is a source of high inter-individual variability due to the poor oral bioavailability of pitolisant in rats (1.5%). Drug abuse liability studies were conducted and evaluated as part of the toxicology section.

Since the secretion of endogenous histamine from enterochromaffin-like cells of the stomach is involved in the trigger of HCl secretion and is partly controlled by H3R, specific studies were performed with an acetylcholine esterase inhibitor, rivastigmine, which is known to increase gastric acid secretion. Pitolisant at up to 10 mg/kg p.o did not induce gastric ulcer when given alone or in combination with rivastigmine. Since rivastigmine alone did not induce gastric ulcer in the experimental conditions of this assay, a conclusion on the lack of potentiation of rivastigmine's effect on gastric mucosa is questionable. Pitolisant did not affect gastric secretion volume and gastric acid secretion in the Shay ulcer model, contrary to cimetidine.

Pharmacodynamic drug interactions

In animal models, synergistic effects of pitolisant with olanzapine were shown as regards their ability to block the hyperlocomotion induced by D-amphetamine or MK-801, and apomorphine-induced climbing behaviour. In the latter case, a synergistic effect was also shown with risperidone. The combination of pitolisant with rivastigmine enhanced the ability of both compounds to increase extracellular acetylcholine levels. Some interactions were found with lisuride and ropinirole (D2 agonists used in the treatment of PD), but were assessed to be caused by PK interactions.

2.3.3. Pharmacokinetics

The non-clinical pharmacokinetics (PK) and the associated absorption, distribution, metabolism, and excretion (ADME) properties of pitolisant were studied in relevant toxicity species. *In vivo* studies were carried out by the oral route of administration as this is the proposed therapeutic route in humans and also by the intravenous (IV) route to assess the bioavailability in animals.

Analysis

Analytical methods were developed to quantify pitolisant and its major metabolites in rats, dogs, mice, and monkeys. All the LC-MS or UV analytical, quantitative methods were adequately validated.

Absorption

In vitro, pitolisant was found to have high permeability and no significant efflux. In addition, pitolisant has a high solubility at pH 1.0 and 6.8, and a high stability in simulated gastric and intestinal fluids. Therefore, pitolisant can be classified as BCS class I and its intestinal permeability is not expected to be a limiting factor to its absorption in humans.

In rats, orally dosed with [^{14}C]-pitolisant, the bioavailability was only 1.5% when unchanged pitolisant was considered and nearly 100% when total [^{14}C] was considered. This can be explained by an active first-pass metabolism. The maximum concentration (Cmax) was reached after 15 minutes and apparent elimination half-life ($T_{1/2}$) of pitolisant in plasma was approximately 3 h following oral administration. The apparent volume of distribution (Vss) of pitolisant at steady state (6378 mL/kg) was approximately 10-fold greater than total body water in rats, indicating extensive tissue distribution of pitolisant. Following IV administration, the clearance (CL) of pitolisant from plasma was 8163 mL/h/kg, which is approximately 2.5-fold greater than the hepatic blood flow rate in rats (approximately 3300 mL/h/kg), suggesting an active extraction of the parent from the circulating blood. In Cynomolgus monkeys, the oral bioavailability of unchanged pitolisant in plasma was 27% and nearly 100% when total [^{14}C] was considered. Apparent elimination $T_{1/2}$ of pitolisant in monkey plasma was about 7.5 h. Following repeated dosing, exposure increased in a more or less dose-proportional manner in the preclinical species with no or moderate accumulation.

Distribution

Pitolisant was highly bound to serum protein in human (91% – 96%), monkey (95% – 97%), dog (91% – 93%), rat (88% – 91%) and mouse (91% – 93%). Over the concentration range of 10 nM to 1 µM, the main human metabolites (BP2.951, BP1.8054, BP1.9733, BP1.3473, BP1.3484, BP1.10749 and BP1.10556) exhibited serum protein binding comparable to pitolisant. No major differences in serum protein binding were seen between animals and human.

Pitolisant demonstrated some red blood cells partitioning (~30%) over the clinically relevant concentration range (blood to plasma ratio was 0.75 - 0.88 at 0.01 - 1 µM). A similar red blood cell partitioning was found for its main metabolites (BP2.951, BP1.8054, BP1.9733, BP1.3473, BP1.3484, BP1.10749 and BP1.10556) with blood to plasma ratio's ranging from 0.5 up to 1.0 indicating no or partial red blood cells partitioning (~40%) except for the metabolite BP1.8186, which demonstrated a high blood cell partitioning (~60%) with an average blood to plasma ratio of 1.4.

Tissue distribution studies revealed that pitolisant was widely distributed into the body in all the tested species. In mice, pitolisant was mainly distributed in liver, lung, kidney and bile. In rats, drug-related radioactivity was widely distributed with the highest concentrations found in GI tract and tissues of elimination with significant ones in the liver and kidney. Distribution to melanin containing structures (skin, uveal tract) was also reported in partially pigmented rats and was retained for up to 35 days. In male Cynomolgus monkeys, high radioactivity levels were identified in GI tract, bile, liver, kidneys, seminal vesicles and prostate.

In pregnant rats [^{14}C]-pitolisant crosses the placenta into the foetus, where [^{14}C]-radioactivity was about 2-fold lower than in maternal blood and declined with similar half life. In lactating female rats [^{14}C]-pitolisant was found in milk at levels 1.1- up to 4-fold the levels found in plasma.

Metabolism

In vitro and *in vivo* studies were performed to investigate the metabolism of pitolisant across species. *In vitro* metabolism studies of pitolisant using microsomes and hepatocytes from rat, dog, monkey and human, have shown that the two major non-conjugated metabolites were BP2.941 and BP2.951 in monkeys and humans but not in rat. Other oxidised metabolites of pitolisant such as BP1.2525 and BP1.2526 were present but to a minor extent.

In vivo, pitolisant is extensively metabolised in mice, rats, monkeys and humans with the primary route through oxidation in various positions and cleavage of the molecule followed primarily by glycine, O-glucuronide and to a lesser extent sulphate conjugation. Relative abundance differed among species with cleaved forms of pitolisant leading to inactive metabolites.

In mice, the major plasma metabolites were cleaved forms of pitolisant, leading to inactive carboxylic acid metabolites (BP1.3484, BP1.3473, BP1.10749). In monkeys, the major plasma metabolites were acid metabolites of piperidine ring-opened pitolisant (BP2.951, BP1.8186) and glucuronides of hydroxylated pitolisant (a.o. BP1.9733). The metabolism in rats differed from mice, monkeys and humans because the major metabolites were mostly conjugated ones secondary to oxidation but a non-conjugated oxidative metabolite such as BP1.2526, hydroxy-pitolisant, and to a lesser extent BP1.2525, a ketone pitolisant were also present.

In humans, the metabolite profile was evaluated using two different [^{14}C]-radiolabels of pitolisant. The first radiolabel was located in a labile position, generating [^{14}C]-CO2 (22%), upon metabolism. In this study, BP1.8054, a glycine conjugate, and BP1.9733, a glucuronide, were the main circulating metabolites but there were also several unidentified components that constituted significant portions of radioactivity. Using the second more stable [^{14}C]-radiolabel one circulating major metabolite, BP1.3484,

was most prominent across all individuals, while three other metabolites (BP1.10749, BP1.3473 and BP1.8054) were only major in some individuals.

In general, mice, monkeys, and humans seemed to share similar metabolic pathways, but it should be noted that the metabolite BP1.8054, a glycine conjugate of a phase I metabolite, was only detected in plasma of humans and in the urine of mice but not in monkeys nor rats. The toxicity of this metabolite was, therefore, assessed in a separate toxicity study.

The pharmacological activity of the main metabolites over human H_3 receptors revealed that only BP1.2526 and BP1.2525 at a lesser extent have an affinity towards human H_3 receptor and all other human metabolites were inactive.

In vitro data suggest that CYP3A4 and CYP2D6 are the predominant pathways for the oxidative metabolism of pitolisant. In vitro, pitolisant and all measurable metabolites were not significant inhibitors of CYP1A2, CYP2C9, CYP2C8, CYP2C19, CYP3A4, UGT1A1, UGT1A4, UGT1A6, and UGT1A9. Pitolisant inhibits CYP2D6 with an IC50 of 2.6 µM.

Excretion

Excretion/elimination was characterised in mass-balance studies performed after oral and intravenous dosing in rats and monkeys. In the rat, following oral and intravenous administration, there was high recovery of radioactivity within the collection period (98 and 93%, respectively) with a majority of the radioactivity in urine (49% and 32%, respectively, including cage wash) and faeces (45% and 56%, respectively). Some difference was reported in function of the route; however, there were both urinary and biliary excretions following oral and intravenous administration with low levels of radioactivity detected in expired air (3.6% (oral) and 4.4% (I.V.)). Using a more stable label, a similar high recovery (97%) with 44% in urine and 52% in faeces was found, while only 0.4% was expired to air.

Following oral and intravenous administration of [^{14}C]-pitolisant to monkeys, the majority of the dose was recovered in urine (70% and 63%, respectively, including cage wash). As less than 5% of the dose was recovered in the faeces up to 168 h post-dose (both administration routes), it can be concluded that biliary elimination was a minor route of excretion. The presence of expired [^{14}C]-CO_2 indicates that formation of [^{14}C]-CO_2 is occurring (~8.5% of the administered dose over the 0-24h period), which accounts for most of the shortfall in recovery.

Similar results were found in humans given the non-stable [^{14}C]-pitolisant (20 mg, po), yielding mainly renal excretion (63%), while 2.5% of administered radioactivity was recovered in faeces and the amount excreted via expired air was calculated to be 22.6%.

2.3.4. Toxicology

Single and repeat dose toxicity

The acute toxicity of pitolisant was evaluated by the oral and intravenous route in mice and rats. In mice, the no-effect dose was > 30 mg/kg orally and > 5 mg/kg, i.v., with a maximum non-lethal oral dose of 100 mg/kg. The minimum lethal doses were 150 mg/kg, p.o. and 10 mg/kg, i.v. In rats, the no-effect dose was > 50 mg/kg, orally and 12 mg/kg, i.v., with a maximum non-lethal oral dose of 100 mg/kg.

The single-dose toxicity studies demonstrated the central nervous system to be the main target organ. One of the metabolites tested, the BP1.2526, was shown to be a convulsant. In repeated doses studies, effects were observed at the highest doses in the central nervous system (hypoactivity, ptylalism, abnormal gait, tremors and clonic convulsions) of mice, rats and monkeys. Reversible changes in some organ weights and limited histopathological changes in some organs in rodents (liver, duodenum, thymus, adrenal gland and lung) were recorded. The NOAEL by oral route were 75, 30 and 12 mg/kg/day

in mice, rats and monkeys, respectively with safety margins based on AUC for male and female of 9, 1 and 0.4, respectively.

A comparison of non-clinical and clinical metabolism data showed that one metabolite of pitolisant, BP1.8054, occurred only in humans as a major metabolite. The toxicology data for BP1.8054 showed no activity on human and rat recombinant H3 receptor; it was also inactive on hERG channel. It showed no genotoxicity *in vitro* in an Ames test and a micronucleus test on human lymphocytes. In a 14-day study, it was well tolerated up to several hundred times the human exposure at 20 mg/day and only induced haematological and biochemical modifications. In the 13-week study, BP1.8054 did not induce any significant toxic effect up to the dose of 300 mg/kg/day representing several hundred times the human therapeutic exposure. In the embryofoetal development study, no significant toxicity and no teratogenicity was observed up to several hundred times the human therapeutic exposure.

Toxicokinetic data

Regarding the metabolites, evidence of exposure of the main human metabolites (BP2.951, BP1.8054, BP1.9733, BP1.3473, BP1.3484, BP1.10749 and BP1.10556) were shown in mice, rats and monkeys, with the exception of BP1.8054, a glycine conjugate of a phase I metabolite. BP1.8054 was only detected in the plasma of humans and in the urine of mice but not in monkeys nor rats. The toxicity of this metabolite was, therefore, assessed in a separate toxicity study and was without any significant toxic effect at several hundred times the human therapeutic exposure. BP2.951, BP1.2526 were compared to pharmacokinetic parameters of pitolisant in humans at a therapeutic dose of 20 mg per day. BP2.951 metabolite was measured during clinical trial P03-03 (at 40 mg per day). For this metabolite, the safety margins based on AUC (at NOAEL) were in mice, rats and monkeys for male and female: 3.7/2.4, 0.96/1.9 and 6.5/6.5, respectively. The BP1.2526 and BP1.2525 were measured in the P03-03 clinical study and were found at very low levels (trace levels). The major human phase I metabolites BP1.3473 and BP1.3484 were found in 9-month monkey samples and in the mouse (14-day toxicity and carcinogenicity study) at satisfying safety margins (>17x). Furthermore, the major glucuronide metabolite (BP1.9733) in human species was measured in monkey (9-month) samples leading to satisfying safety margins (>25x).

Genotoxicity

Pitolisant and two metabolites (BP1.2526, BP2.951) did not cause any gene mutation in Ames test in the absence or presence of microsomal activation at concentrations up to cytotoxic levels. In the MLA assay, pitolisant did not induce gene mutation or chromosomal damage when tested up to cytotoxic concentrations in the presence or absence of microsomal activation. Concerning the *in vivo* studies, in the micronucleus test, no increase in the number of micronucleated erythrocytes (MPE/PET) was observed in Swiss mice treated at 150 mg/kg of pitolisant per os with evidence of exposure. This indicates that the test compound has no potential to cause genotoxic effect up to the maximum dose of 150 mg/kg.

BP1.8054, a major metabolite only present in humans, showed no genotoxicity *in vitro* in an Ames test and a micronucleus test on human lymphocytes.

New studies were submitted reporting on the mutagenicity of several human pitolisant metabolites: BP1.10556, BP1.3473, BP1.3484, BP1.8186, and BP1.10749. All metabolites tested negative in the Ames assay, and they are therefore without mutagenic potential.

Carcinogenicity

Two carcinogenicity studies were conducted to evaluate the potential carcinogenicity of orally administered pitolisant in mice and rats.

Pitolisant did not reveal any neoplastic potential up to a level of 30 mg/kg/day and 75 mg/kg/day in rats and transgenic mice. Taking into account the proposed maximum clinical dose of 36 mg, the safety margins based on the AUC were 1.9 and 11 in rats and mice, respectively.

Reproduction toxicity

In a fertility study in rats, there was reduced sperm motility (4/22 and 4/23 males at 90 and 52 mg/kg/day, respectively). Sperm morphological alterations occurred at 90 and 52 mg/kg/day (18% and 17% of males respectively). The main alterations were sperm with isolated head, misshapen head, bent tail and degenerating tail, but these changes did not affect fertility in males. In view of the results, 30 mg/kg/day was considered to be the NOAEL for both sexes. Therefore, the safety margin calculated taking into account AUC was around 1 in males and females.

Embryofoetal toxicity of pitolisant was evaluated in rats and rabbits following administration during the organogenesis period. In rat treated with 30, 52, 90 and 110 mg/kg/day, no mortality was recorded in females. A slight decrease in body weight was reported at doses of 30, 90 and 110 mg/kg/day. A statistically significant decrease of food consumption was observed at 90 and 110 mg/kg/day. There were no statistically significant related treatment foetal malformations up to 110 mg/kg/day. Maternal toxicity and foetal weight reductions were noted at 90 and 110 mg/kg. NOAELs were 52 and 90 mg/kg for females and litters, respectively. The safety margins at 52 and 90 mg/kg were of 0.6 and 2.3, respectively.

In rabbits treated by oral dose at 30, 67 and 150 mg/kg/day, there were at 150 mg/kg the following clinical signs in dams: pronounced decreased food consumption, a slight diminution of body weight. In litters, at 150 mg/kg, slightly delayed ossification, anasacarna, acaudate, cleft palate and cerebral ventricle in foetuses were reported. These malformations were observed with maternal toxicity. The NOAEL for both females and litters was 67 mg/kg (safety margins based on AUC <0.2). Taking into account the limited exposure to pitolisant by oral route administration, another study was carried out by intramuscular (IM) route.

In an additional study performed in rabbit by IM route at 4, 8 and 16 mg/kg, a general retardation in skeletal development was observed at 16 mg/kg, but this effect was associated with the maternal toxicity. The NOAEL for dams and foetuses were 4 and 8 mg/kg, respectively. The safety margins are 0.6 for the dose of 4 mg/kg and 1.3 for the dose of 8 mg/kg. Nevertheless, in this study, foetal examination at terminal necropsy on DG29 revealed at that at 16 mg/kg/day pre-implantation loss was slightly increased and both the number of implantations and the number of live foetuses was decreased. Skeletal examination revealed an increased incidence of foetuses fused sternebrae and with findings indicative of retardation in foetal development (supernumerary rib(s), incomplete / unossified median phalanx of the forepaw and/or 1st metacarpal(s)), at 16 mg/kg/day, but not at 4 or 8 mg/kg/day. The retardation in skeletal development was claimed to be associated with maternal toxicity.

In the pre-natal and post-natal development study conducted in the rat using the oral route of administration, potential treatment-related effects were investigated in the F0, F1 and F2 generations. In the F0 generation, at 90 mg/kg (top-dose) there were 9 deaths recorded at the end of pregnancy, of which 7 were attributed to dystocia during delivery. In this group, most animals showed clinical central nervous system signs. Body-weight gain was reduced as well as food consumption. At 52 mg/kg and 30 mg/kg, no mortality and no noteworthy clinical signs were recorded. In the top, dose-group surviving females did not produce milk and did not nurse their pups, which all died or were eaten by the mothers. In the mid-dose-group (52 mg/kg) some alterations in maternal behaviour were recorded in two females. One female had no milk and did not nurse for 3 days, and its pups died. In the F1 generation, at 90 mg/kg there was a reduction of live-born pups and an increase of post-implantation losses and dead-born pups. After delivery, surviving pups died within 4 days postpartum. Eighteen pups from 4 litters showed a major malformation (cleft palate), and 5 pups from 2 litters showed a minor malformation

(abnormal flexure of the extremities). Among the 52 mg/kg litters the viability index on day 4 postpartum was slightly reduced (5%). During the first days postpartum, physical and motor developments were slightly reduced at 52 mg/kg. Pup size and physical development were slightly reduced until day 30 postpartum. Motor development (postural reflex and righting tests) was delayed between day 1 and day 17 of lactation.

Taken together, these results indicate that pitolisant had effects on reproductive function and embryofoetal development at clinically relevant exposures. These results and precautions for use in pregnant and breast-feeding women have been reflected in appropriate sections of the SmPC.

Juvenile toxicity

In juvenile toxicity studies in rats, mortality and convulsions were observed at highest doses by intraperitoneal route (30 and 60 mg/kg). There was no effect on the reproductive and development function of the treated animals. Pathological changes were limited to a slight increase of alveolar macrophages in the lungs at two doses of 30 and 60 mg/kg. The NOAEL was 15 mg/kg for male and female rats with a safety margin based on the AUC of 1.8 and 1, respectively.

Local Tolerance

As the intended administration route is oral, the CHMP agreed that no local tolerance studies are necessary.

Other toxicity studies

Antigenicity

Pitolisant is a new chemical entity of low molecular weight and of non-peptidic nature. It is unlikely that any antigenicity potential appeared following the chronic administration. Therefore, antigenicity aspects were not investigated further.

Immunotoxicity

Chronic administration (6 months in rats, 9 months in monkeys) evidenced no significant change on the following parameters: haematology, immune system organ weights and histology, frequency of infections and tumours including in the two carcinogenicity studies. Therefore, immunotoxicity aspects were not investigated further.

Abuse potential and dependence

Regarding the abuse potential, studies (discrimination, conditioned-place preference, locomotor sensitization and self-administration) were performed in several species (rodents and primates), by several routes of administration (IV, SC, i.p., p.o.), at different doses including high doses, and with negative and positive control groups (modafinil, cocaine, and vehicle saline). The dependence potential of pitolisant was assessed in rats with morphine, cocaine or amphetamine as a positive reference. The Gellert-Holzmann scale, anxiety and depression behavioural tests and physical indices (body weight, temperature) were used to assess withdrawal symptoms. Results were not in favour of an abuse and dependence potential of pitolisant, except for the self-administration study in rhesus monkeys, as the higher pitolisant tested dose served as a reinforcer for 2 of the 4 monkeys. In the self-administration study, there were two test conditions with individual monkeys (M1288 and M1344) in which mean numbers of pitolisant infusions obtained exceed those of saline, and their range did not overlap at 0.3 mg/kg. However, the mean number of pitolisant infusions were below saline levels at 0.56 mg/kg, the highest dose tested. Although these two monkeys seem to present an increase in the mean infusion at 0.3 mg/kg of pitolisant during regular testing, an additional saline test condition conducted at the end of the study as is usual in such studies showed numbers of infusions which overlap the 0.3 mg/kg dose

for monkey M1288 and was similar to the 0.3 mg/kg dose for monkey M1344. No conclusion could be drawn.

For tolerance, the Applicant did not provide a dose-effect curve but the changes in t-MeHA brain level, a reliable index of the activation of the histaminergic neurons via histamine H3 receptors measured in the brain 90 min after a single oral administration of vehicle or pitolisant to mice following a 4-, 10- and 17-day subchronic treatment. Results showed a significant decrease in the t-MeHA level as compared to control mice, 17 hours after the last pitolisant administration following a 4-day subchronic treatment. However, the decrease in the t-MeHA level observed following 10-day and 17-day subchronic treatment was non-significant. No conclusion on tolerance could be drawn.

In the literature, reinforcing effects of sigma receptor agonists in rats that had a history of cocaine self-administration has been reported, while some review focused on the potential of sigma receptor antagonists as treatments for stimulant abuse. Additionally, sigma receptor agonists were found to increase dopamine concentrations in the nucleus accumbens shell. In view of the binding affinities of pitolisant for histamine non-H3R and for a series of non-histamine receptors, the Applicant concluded to a good selectivity profile of pitolisant for the H3R. However, pitolisant binds to sigma 1 and 2 receptors with similar or higher affinity than to H3R. It acts as an agonist to sigma-1 and antagonist to sigma-2 with functional IC50 values of 402 nM and 10 µM, respectively. The data do not exclude a risk of abuse potential.

Furthermore, according to pitolisant capacity to increase memory performance and the duration of acquisition of animals, diversion of pitolisant to increase intellectual performance was considered as a potential risk in humans.

Studies on impurities

No impurities have been found higher than the qualification threshold of the ICH 3QA guideline on impurities in new drug substances. Other impurities with structural alert were not found higher than the threshold of toxicological concern concept of 1.5 µg per day (CPMP/SWP/5199/02-June 25, 2006).

Photosafety

As pitolisant does not absorb light in the UVA, UVB and visible range, further investigation of photosafety was not conducted.

2.3.5. Ecotoxicity/environmental risk assessment

Table 1

Substance (INN/Invented Name): Pitolisant			
CAS-number (if available):			
PBT screening		Result	**Conclusion**
Bioaccumulation potential- log K_{ow}	OECD107	-0.11 (pH 5) 1.61 (pH 7) 4.1 (ion corrected log D_{ow})	Potential PBT: N
PBT-assessment			
Parameter	**Result relevant for conclusion**		**Conclusion**
Bioaccumulation	log K_{ow}	4.1 (ion corrected log D_{ow})	not B
	BCF	study not required	-
Persistence	ready biodegradability	not readily biodegradable	P/not P
	DegT50	P.M.	study is required

Toxicity	EC10 algae EC10 crustacea EC10 fish	0.025 mg/L 0.035 mg/L 0.028 mg/L			T
	CMR	not investigated			-
PBT-statement :	The compound is not considered as PBT nor vPvB				
Phase I					
Calculation	**Value**	**Unit**			**Conclusion**
PEC $_{surfacewater}$, default	0.11	µg/L			> 0.01 threshold: Y
Phase II Physical-chemical properties and fate					
Study type	**Test protocol**	**Results**			**Remarks**
Adsorption-Desorption	OECD 106	$K_{oc\ sludge}$ 103, 579 L/kg $K_{oc\ soil}$ 488, 1380, 4036 L/kg			
Ready Biodegradability Test	OECD 301 B	not readily biodegradable			
Aerobic and Anaerobic Transformation in Aquatic Sediment systems	OECD 308	P.M.			study is required
Phase IIa Effect studies					
Study type	**Test protocol**	**Endpoint**	**value**	**Unit**	**Remarks**
Algae, Growth Inhibition Test/*Pseudokirchneriella subcapitata*	OECD 201	EC10	25	µg/L	growth rate
Daphnia sp. Reproduction Test	OECD 211	EC10	35	µg/L	reproduction
Fish, Early Life Stage Toxicity Test/*Brachydanio rerio*	OECD 210	EC10	28	µg/L	survival
Activated Sludge, Respiration Inhibition Test	OECD 209	EC10	29.9	mg/L	respiration
	OECD 209	EC10	8.5	mg/L	respiration
Phase IIb studies					
Sediment dwelling organism *Chironomus riparius*	OECD 218	NOEC	≥425	mg/kg	emergence and development, normalized to 10% organic carbon

Pitolisant is considered not to be PBT, nor vPvB.

A risk to the STP, surface water and groundwater, sediment and soil, is not anticipated based on the prescribed use of pitolisant.

A study on biodegradation in a water-sediment system according to OECD TG 308 is required but not available. As the logDow is above 3, according to the guideline on the environmental risk assessment of medicinal products for human use (EMEA/CHMP/SWP/4447/00 corr 2) a bioaccumulation study in accordance with OECD TG 305 should also be submitted. These two studies will be submitted post-approval and are due in Q4 2021.

2.3.6. Discussion on non-clinical aspects

The pharmacological profile of pitolisant has been described previously in the context of Wakix marketing authorisation.

No additional primary pharmacology studies were performed to support the use of pitolisant in treatment of excessive daytime sleepiness in patients suffering from OSA, with or without CPAP. The rationale for its use is solely based on pitolisant's properties to increase wakefulness, which may counteract excessive daytime sleepiness.

Some additional secondary *in vitro* pharmacology data were submitted. These data supported the specificity of pitolisant for H3R.

Additional cardiovascular safety pharmacology studies confirmed that pitolisant has the ability to prolong the QT interval. *In vitro*, it blocked hERG currents with an IC50 of 1.3 µM and affected action potential parameters in rabbit Purkinje fibres with effects suggesting that it blocks sodium, calcium and potassium channels at concentrations higher than 1 µM. *In vitro* data on major human metabolites show no significant hERG channel blocking activity.

The non-clinical pharmacokinetics (PK) and the associated absorption, distribution, metabolism, and excretion (ADME) properties of pitolisant were studied in relevant toxicity species. These data were assessed in the previous application and considered adequate, apart from the assessment of the metabolism of pitolisant, where it was found that a large part (22%) of the excreted label was expired [^{14}C]-CO_2. Therefore, new studies were performed using a more stable radiotracer. This new radiotracer resulted in a different metabolite profile and new information with respect to the analytical methods, absorption, distribution, metabolism and excretion part. The information from the more stable tracer has been assessed and is integrated in the current PK section. No new matters of concern are raised.

Pitolisant has a known toxicological profile; therefore, no new toxicity studies were submitted in the current procedure apart from mutagenicity assay on several metabolites. Metabolites BP1.10556, BP1.3473, BP1.3484, BP1.8186, and BP1.10749 tested negative in the Ames assay, and they are therefore without mutagenic potential.

Regarding the environmental risk assessment, the dossier is incomplete. The following studies (including reports) will be submitted post-approval:

- Aerobic and anaerobic transformation in aquatic sediment systems (OECD 308)
- Bioaccumulation in Fish: Aqueous and Dietary Exposure (OECD 305)

Considering the risk to the sediment, it can be concluded that there is no risk to the environment.

The non-clinical data are reflected appropriately in the SmPC.

2.3.7. Conclusion on the non-clinical aspects

Non-clinical data show that pitolisant increases wakefulness through its antagonist/inverse agonist action on the H3R, which may counteract excessive daytime sleepiness.

The additional pharmacological, pharmacokinetic and toxicological data that were submitted did not raise new safety concerns.

A study on biodegradation in a water-sediment system according to OECD TG 308 and bioaccumulation study in accordance with OECD TG 305 are requested to be submitted post-approval in Q4 2021.

The CHMP agreed that the available non-clinical data are acceptable to support the application.

2.4. Clinical aspects

2.4.1. Introduction

GCP

The Clinical trials were performed in accordance with GCP as claimed by the applicant.

The applicant has provided a statement to the effect that clinical trials conducted outside the Community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

- Tabular overview of clinical studies

Table 2

Study	Type	Population	Dose and objective
P02-02	PK/PD	Healthy male volunteers (N=36)	Single dose of 1, 5, 10, 20, 40 and 60 mg To assess the pharmacokinetic profile of pitolisant by measuring serum and urine levels
P03-01	BA/PK	Healthy male volunteers (N=8)	Single dose of 20 mg To assess relative bioavailability from two different formulations of pitolisant and to assess the effect of grapefruit juice on the PK profile of pitolisant
P03-03	PK/PD	Healthy male volunteers (N=8)	Repeated dose of 40 mg for 9 days To investigate the PK and PD (feeding behavior and satiety) of pitolisant following repeated dosing
P03-04	PK/PD	Healthy male volunteers (N=12)	Single dose of 90 and 120 mg To assess the pharmacokinetic profile of pitolisant and BP2.951 (inactive metabolite) by measuring serum and urine levels
P03-08	PK/PD	Healthy male volunteers (N=6)	Single dose of 60 mg DDI study with olanzapine
P04-06	PK	Healthy male volunteers (N=6)	Repeated dose of 40 mg from Day 1 to 14 and 50 mg from Day 15 to 28 To assess the PK profile of pitolisant and BP 2.951 at steady state by measuring serum and urine levels
P09-12	PK	Healthy elderly and young adult male and female volunteers (N=25)	Repeated dose of 20 mg for 14 days To investigate the effect of age on the PK parameters of pitolisant
P09-13	PK	Male and female subjects with normal and impaired renal function (N=25)	Single dose of 20 mg To investigate the effect of renal impairment on the PK of pitolisant and its metabolite BP2.951
P09-14	PK	Male and female subjects with normal and impaired hepatic function (N=21)	Single dose of 20 mg To investigate the effect of hepatic impairment on the pharmacokinetics of pitolisant and its metabolite BP2.951
P11-01	PK/PD	Healthy male volunteers (N=6)	Single dose of 20 mg To determine the mass balance recovery after a single oral dose of [^{14}C]-pitolisant and the routes of [^{14}C]-pitolisant metabolism and excretion. In addition, to assess the PK of major metabolites in serum.
P11-03 Part I	PK	Healthy male volunteers (N=12)	Single dose of 20 mg Comparative bioavailability study of a single administration of pitolisant administered with or without concomitant food intake
P11-03 Part II	PK	Healthy male volunteers (N=18)	Single dose of 20 mg DDI study with itraconazole
P11-03 Part III	PK	Healthy volunteers (N=19)	Single dose of 20 mg DDI study with paroxetine
P11-10	PK	Healthy male volunteers (N=18)	Single dose of 20 mg DDI study with rifampicin
P16-02	PK/PD	Healthy, non-dependent recreational stimulant users (N=40)	Single dose of 40 and 240 mg To determine the PK parameters of pitolisant To evaluate the abuse liability of pitolisant

P05-03	PK/PoC	Patients with narcolepsy (N=22)	Repeated dose of 40 mg once daily for 7 days Blood sampling was used to assess compliance.
P06-06	PK/PoC	Patients with narcolepsy (N=26)	Repeated dose of 10 mg once daily in week 1, 20 mg once daily in week 2, and 10, 20 or 40 mg in week 3 and 4 based on efficacy and safety To investigate the exposure to pitolisant and BP2.951
P09-11	PD	Healthy male and female volunteers (N=58)	Single dose of 40 and 120 mg To evaluate the relationship between the PK parameters and the QTcF values
P14-05	PD	Healthy male volunteers (N=24)	Single dose of 160, 200 and 240 mg To evaluate the relationship between the PK parameters and the QTcF values
P14-07 Part I	PK	Healthy male volunteers (N=16)	Single dose of 40 mg DDI study with sodium oxybate (Xyrem®)
P14-07 Part II	PK	Healthy male volunteers (N=16)	Single dose of 40 mg DDI study with modafinil (Modiodal®)
P15-02	PK	Healthy male volunteers (N=8)	Repeated dose of 20 mg To assess the mass balance recovery of a single oral dose of [^{14}C]-pitolisant administered following 7 days of repeat dosing with unlabeled pitolisant and to determine the routes and rates of elimination of [^{14}C]-pitolisant. To further explore the oral PK of a tablet formulation of pitolisant and its known major metabolites (BP2.951, BP1.8054 and BP1.9733) after single and multiple dosing in CYP2D6 genotyped subjects.
P15-15 Part I	PK	Healthy male volunteers (N=18)	Repeated dose of 40 mg from Day 7 to Day 18 DDI study with midazolam and bupropion with pitolisant as inducer
P15-15 Part II	PK	Healthy male volunteers (N=18)	Single dose of 40 mg DDI study with probenecid (UGT inhibitor) with pitolisant as victim
P14-08	PD	healthy volunteers (N=6)	Single dose of 40 mg To evaluate occupancy of the Histamine H3 receptor
P04-01	PK/PoC	Patients with moderate to severe OSA (N=12)	Repeated dose of 40 mg for 3 days To determine the PK parameters of pitolisant To evaluate the efficacy/safety of pitolisant in OSA
P05-01	PK/PoC	Patients with moderate to severe OSA (N=21)	Repeated dose of 40 mg for 8 days To determine the PK parameters of pitolisant To evaluate the efficacy/safety of pitolisant in OSA
P09-16	Dose finding	Patients with moderate to severe OSA (N=116)	Repeat doses of 5 mg, 10 mg, 20 mg and 40 mg Dose finding study
P09-8 HAROSA-I	Efficacy/ safety	Patients with moderate to severe OSA using nCPAP (N=244)	Repeat doses of 20 mg pitolisant To evaluate the efficacy/safety of pitolisant in OSA patients who use nCPAP but still complain of EDS
P09-09 HAROSA-II	Efficacy/ safety	Patients with moderate to severe OSA refusing nCPAP (N=268)	Repeat doses of 20 mg pitolisant To evaluate the efficacy/safety of pitolisant in OSA patients who complain of EDS and refuse nCPAP.

[A] by assessor

EDS= excessive daytime sleepiness, nCPAP= nasal continuous positive airway pressure ,OSA= obstructive sleep apnea, PD= pharmacodynamics, PK= pharmacokinetics, PoC= proof of concept

2.4.2. Pharmacokinetics

Pitolisant has been approved as Wakix® for the treatment of narcolepsy on the 19th of November 2015. Current MAA is for the treatment of Excessive Daytime Sleepiness (EDS) in patients with Obstructive Sleep Apnoea (OSA) and treated by Continuous Positive Airway Pressure (CPAP) but still complaining of EDS, or in patients with OSA refusing/not tolerating CPAP. The recommended dose is 18 mg pitolisant once daily in the morning during breakfast. The dose could be reduced to 9 mg or 4.5 mg pitolisant once daily based on efficacy. The majority of clinical pharmacology studies have been described in the context of Wakix evaluation so this report will focus on new studies.

In addition to the studies previously submitted for Wakix, PK studies in healthy volunteers (studies **P09-11**, **P14-05**, **P14-07**, **P15-02** and **P15-15**) and patients (studies **P04-01** and **P05-01**) were submitted

for current MAA. The PK in patients could not be compared to that in healthy volunteers because only 1 blood sample was obtained 3 h after dosing. No significant differences in PK are expected between the patient population and healthy volunteers because the disease is not expected to influence the absorption, metabolism and excretion of pitolisant.

Furthermore, no new studies were performed at dosages of 4.5 and 9 mg pitolisant. Therefore, the PK of pitolisant at a dose of 4.5 and 9 mg pitolisant has only been investigated in one study and in a very limited number of subjects (N=5 per dose) with high inter-individual variability. The limited PK data over the clinical dose range of 4.5 to 9 mg pitolisant hampers the exposure-response relationship.

Analytical method

Pitolisant was analysed in serum and urine using high-performance liquid chromatography (HPLC) or ultra-performance liquid chromatography (UPLC) coupled with tandem mass spectrometry (MS/MS). The analytical methods used to determine pitolisant in serum and urine appear to be sufficiently validated. The LLOQ ranged from 0.1 to 1 ng/mL between the different analytical methods.

Population PK (PopPK) Modelling

A new PopPK model was developed for pitolisant with 320 healthy subjects from 13 phase I trials (P02-02, P03-03, P04-06, P09-11, P09-12, P11-03, P11-10, P14-05, P14-07, P15-02, P15-15 and P17-03), resulting in 5450 pitolisant serum concentrations. Furthermore, 29 patients from two pilot OSA phase 2 trials were included (P04-01 and P05-01), but only a trough concentration was available. This dataset contains information about single-dose administrations ranging from 10 mg to 240 mg and multiple-dose administrations of 20, 40 and 50 mg. Plasma concentrations below the lower limit of quantification (n = 241) were retained in the model by adjustment of the maximum likelihood function. A three-compartment model with zero-order absorption best described the distribution component of the pharmacokinetics. Furthermore, an effect of gender on the zero-order absorption rate constant was observed. Inter-individual variability was included on T_{lag}, k0, F, V1, Q2, Q3, V3, CL, K_{enz}, $IC_{50,}$ and a combined error model described the residual variability. The parameter estimates indicate that CV is extremely high for K_{enz} and V3, which questions the 3rd compartment and also the approach to describe the time-dependency in the pharmacokinetics of pitolisant. The enzyme model seems to be quite an empirical solution to a time-varying clearance. The PK of pitolisant seems to be significantly affected by the CYP2D6 genetic polymorphisms (second mass balance study). The CYP2D6 genetic polymorphisms were not determined or reported in most clinical studies and also not included in the PopPK model. The reason for this is unknown.

Physiologically-based pharmacokinetic (PBPK) modelling

A PBPK model is being developed to predict the effect of hepatic impairment on the PK of pitolisant and predict DDIs with pitolisant as victim. The PBPK model did not describe the pharmacokinetics of pitolisant sufficiently accurate. Furthermore, no qualification of the PBPK model was provided for the different CYP2D6 genotypes. These issues indicate that the PBPK model is not suitable to predict the PK of pitolisant.

Absorption

Following oral administration, t_{max} is reached between 2 and 4 hours following dosing. After a single oral dose with pitolisant, C_{max} is 0.99 ng/mL following a 4.5 mg dose, 3.1 ng/mL following is 9 mg dose and ranges between 12.6 and 26.2 ng/mL following a 18 mg dose. The $AUC_{0-\infty}$ is 20.8 ng×h/mL following a 4.5 mg dose, 28.7 ng×h/mL following a 9 mg dose and ranges between 150 and 352 ng×h/mL following a 18 mg dose. The inter-individual variability is ~54% at a clinically relevant dose of 18 mg pitolisant. Steady-state is reached after ~6 days following once daily dosing. Accumulation ratio was 2.2-fold for

C_{max} and 3.0 fold for AUC at a dose of 18 mg pitolisant HCl. No information is available on the accumulation at the clinically relevant doses of 4.5 mg and 9 mg.

Over the clinical dose range of 4.5 to 18 mg pitolisant once daily, the C_{max} and AUC appear more than dose-proportional. However, the number of subjects treated with 4.5 mg and 9 mg is too limited to draw firm conclusions. The exposure appears more or less dose-proportional over a non-clinically relevant dose range of 36 to 216 mg pitolisant.

The absolute oral bioavailability has not determined in humans. Based on the mass balance studies, the absorption appears to be high (~91%). However, the bioavailability is most likely low (7.8-37% based on the two mass balance studies).

The food intake decreases the C_{max} by 25% and increases the t_{max} by 2 hours. However, the AUC remains bioequivalent with or without food. Thus, there is a potential effect of food intake on the bioavailability, but no clinical consequences are expected. Pitolisant is recommended to be taken during breakfast for tolerability.

Distribution

Pitolisant has a serum protein binding of 91.4-95.2% and a plasma protein binding of 93%. The blood-to-plasma ratio 0.75-0.88, indicating that pitolisant does not accumulate in red blood cells.

Pitolisant has a high apparent volume of distribution (1030 to 2884 L). It is unknown what the volume of distribution is, since no absolute oral availability information is available. If the bioavailability is low as expected based on the mass balance studies, than the volume of distribution is high (1.5 to 4.1 L/kg for a subject with a bodyweight of 70 kg and a bioavailability of 10%). This indicates substantial extravascular distribution.

Metabolism

The biotransformation pathway of pitolisant in humans was investigated using *in vitro* and *in vivo* studies. Pitolisant is metabolised by CYP2D6, 3A4 and 3A5 to different metabolites. In subjects that are CYP2D6 intermediate metabolisers, CYP2D6 extensive metabolisers or CYP2D6 ultra-rapid metabolisers and taking no PXR inducers, CYP2D6 is the main enzyme involved in the biotransformation of pitolisant and CYP3A is involved to a lesser extent. In subjects that are CYP2D6 poor metabolisers or are CYP2D6 intermediate metabolisers, CYP2D6 extensive metabolisers or CYP2D6 ultra-rapid metabolisers and taking PXR inducers, CYP3A is significantly involved in the biotransformation of pitolisant and CYP2D6 is involved to a lesser extent.

Table 3

	% in serum	
Compound	**P11-01 (4 h)**	**P15-02 (0-72h)**
parent	?	11%
BP1.3484	ND	58.1%
BP1.9733	17%	<1%
BP1.8054	13%	8.3%
BP1.10749	11.4%	8.1%
BP1.10556	9.9%	7.9%
BP1.3473	ND	9.0%
S15	10.3%	ND
S17	8.0%	ND
S18	13.6%	ND
	% in urine	
	P11-01 (0-72 h)	**P15-02 (0-72h)**
parent		1.3%
BP1.3484		5.1%
BP1.8054	10.4%	12.0%
BP1.10556		22.0%
BP2.951	10.5%	16.9%
BP1.9733		2.8%
BP1.8186		7.8%

Transporters

Pitolisant is not a substrate of P-glycoprotein, BCRP, OATP1B1, OATP1B3, OCT1, MRP1, MRP2 and MRP3 at clinically relevant concentrations.

Excretion

Following oral administration, the majority of the radioactive dose is absorbed and excreted via urine (~89%) and only to a limited extent via faeces (~2.5%). The majority of the eliminated radioactivity was metabolite, indicating extensive metabolism. Pitolisant has an apparent clearance of 87 L/h and an elimination half-life ~12 hours at a clinically relevant dose of 18 mg pitolisant.

Special Populations

Patient population

No conclusions based on PK sampling can be made, and no comparison of the PK can be made with healthy volunteers. No significant differences are expected in the PK between the patient population and healthy volunteers because the disease is not expected to influence the absorption, metabolism and excretion of pitolisant. However, the BMI in patients with obstructive sleep apnoea is expected to be

higher compared to the average healthy volunteer population. The dose-normalised C_{max} tended to decrease with increasing BMI category with no difference in dose-normalised AUC, but the number of subjects with morbid obesity was too limited to draw conclusions. Therefore, the exposure may be lower in the patient population compared to healthy volunteers.

Genetic polymorphisms

The pitolisant exposure depended on the CYP2D6 metaboliser genotype and was lowest in subjects with ultra-rapid genotype and highest in subjects with poor CYP2D6 metabolise genotype. Higher systemic exposure (C_{max} and AUC) was observed in CYP2D6 poor metabolisers compared to CYP2D6 extensive metabolisers (~2.1-fold for C_{max} and ~2.3-fold for AUC). The C_{max} and AUC in subjects with CYP3A5*3 appears to be higher (~1.5-fold) compared to CYP3A5*1. This was not significantly different, but this may be due to the limited number of subjects and the inclusion of subjects that are CYP2D6 intermediate metabolisers, CYP2D6 extensive metabolisers or CYP2D6 ultra-rapid, metabolisers in which CYP2D6 is the main enzyme metabolising pitolisant. The effect of CYP3A4 genetic polymorphisms on the PK of pitolisant is unknown.

Renal impairment

In a clinical renal impairment study, the C_{max} and AUC of pitolisant increase by a factor 2.5 in renally impaired subjects, independent of the renal impairment. Pitolisant is mainly metabolised in the liver (via CYP2D6 and 3A) and only eliminated <2% as parent via urine; no impact on the PK of pitolisant of renal impairment is expected. The observed effect of renal impairment in the clinical study could be due to the inclusion of CYP2D6 poor metabolisers into the renal impaired groups.

Hepatic impairment

In a clinical hepatic impairment study, C_{max} did not increase. The AUC increased 1.4-fold in subjects with mild hepatic impairment and 2.4-fold in subjects with moderate hepatic impairment. Because the CYP2D6 genotype was unknown in the clinical hepatic impairment study, the observed PK of pitolisant may be caused by differences in CYP2D6 genotype.

Gender

The majority of the studies was performed in male subjects. Based on the provided box plots showing the dose normalised C_{max} and AUC of pitolisant, the exposure appears slightly higher in females compared to males. This is most likely due to the lower body weight in females compared to males.

Race

All studies have been performed mainly in Caucasians (Caucasians = 270; Black = 38; Asian = 20; Other = 3). Based on the data provided by the Applicant, the exposure appears to be similar between the different races.

Body weight

The C_{max} appears to decrease with increasing BMI and no effect of the BMI on the AUC. However, the number of subjects with a BMI >30 kg/m^2 is very limited (N=6). Due to the limited number of morbid obese subjects and the high inter-individual variability, it cannot be excluded that the exposure is decreased in morbid obese subjects.

Elderly

An increase of ~1.4-fold was observed in the elderly (68 to 82 years of age) compared to subjects aged 18-45 years. The reason for this increase in exposure is unknown.

Drug-drug interaction (DDI)

Pitolisant as victim

In vitro data indicate that pitolisant is metabolised by CYP2D6, 3A4 and 3A5 and is not a substrate of drug transporters. In subjects that are CYP2D6 intermediate metabolisers, CYP2D6 extensive metabolisers or CYP2D6 ultra-rapid metabolisers and taking no PXR inducers, CYP2D6 is the main enzyme involved in the biotransformation of pitolisant and CYP3A is involved to a lesser extent. In subjects that are CYP2D6 poor metabolisers or are CYP2D6 intermediate metabolisers, CYP2D6 extensive metabolisers or CYP2D6 ultra-rapid metabolisers and taking PXR inducers, CYP3A is significantly involved in the biotransformation of pitolisant and CYP2D6 is involved to a lesser extent. The CYP2D6 phenotype was not determined in the clinical DDI studies.

In a clinical DDI study, the exposure to pitolisant was decreased when concomitantly administered with the PXR inducer rifampicin (induces CYP3A and transporters) and probenecid (UGT, OAT1 and OAT3 inhibitor and maybe inducer of FMO and CYP3A). The exposure decreased ~2-fold in combination with rifampicin and ~1.5-fold in combination with probenecid. The mechanism for the interaction of pitolisant with probenecid is unknown, may be due to induction of FMO or CYP3A. Probenecid is an inhibitor of UGT and the drug transporters OAT1 and OAT3 (Yin and Wang, 2016). Pitolisant is not a substrate for UGT. It is unknown if pitolisant is a substrate of OAT1 and OAT3, but inhibition of OAT will lead to an increase in pitolisant exposure. The information on the induction potential of probenecid towards CYP3A is too limited to conclude that the observed decrease in pitolisant exposure is caused by CYP3A induction.

A clinically relevant DDI was observed when pitolisant was concomitantly administered with a strong CYP2D6 inhibitor. The exposure to pitolisant was increased 2.2-fold. The DDI effect in subjects that are CYP2D6 poor metabolisers and take a CYP2D6 inhibitor is unknown, but most likely lead to no clinically relevant impact on the PK of pitolisant.

No clinically relevant DDI was observed with grapefruit juice (intestinal inhibitor of CYP3A) and itraconazole (hepatic inhibitor of CYP3A) and the frequently co-administered medicinal products olanzapine, sodium oxybate and modafinil. The lack of a DDI with grapefruit juice and itraconazole is most likely due to the inclusion of subjects in who CYP2D6 is the main metabolising route (subjects that are CYP2D6 intermediate metabolisers, CYP2D6 extensive metabolisers or CYP2D6 ultra-rapid metabolisers). In these subjects a CYP3A inhibitor will not have an effect on the PK of pitolisant.

The effect of CYP3A inhibitors on the PK of pitolisant in CYP2D6 poor metabolisers is currently unknown, but may lead to higher exposure and thus safety issues. Therefore, the DDI implication on safety in this subpopulation is unknown and needs to be further investigated in a PAM. In addition, the effect of CYP3A inducers on the PK of pitolisant in CYP2D6 ultra-rapid metabolisers is currently unknown, but may lead to lower exposure and thus efficacy failure. A warning is included in the SmPC and the Applicant is advised to investigate the effect of CYP3A inducers on the PK of pitolisant in CYP2D6 ultra-rapid metabolisers before a dose recommendation can be give to this population.

Pitolisant as perpetrator

In vitro, pitolisant is not an inhibitor of CYP enzymes at clinically relevant systemic concentrations and for CYP3A4 at relevant maximal intestinal concentrations. In addition, pitolisant is not an inhibitor of UGT at clinically relevant systemic and intestinal concentrations. At clinically relevant intestinal concentrations, pitolisant is not an inhibitor of P-glycoprotein and BCRP. At clinically relevant portal vein concentrations, pitolisant is an inhibitor of OCT1, but not of OATP1B1 and OATP1B3. At clinically relevant systemic concentrations, pitolisant may be an inhibitor of OCT1, but not an inhibitor of P-glycoprotein, BCRP, OATP1B1, OATP1B3, OCT2, OAT1, OAT3, MATE1 and MATE2-K. Pitolisant is not an inducer at clinically relevant systemic concentrations but maybe an inducer via CAR at clinically relevant intestinal concentrations (e.g. CYP3A4 and transporters).

In a clinical DDI study, pitolisant reduced the exposure of midazolam (a CYP3A substrate) most likely due to induction of CYP3A. The DDI study indicates that pitolisant should be considered a weak inducer. Based on the *in vitro* data, it is expected that pitolisant is mainly an inducer of intestinal CYP3A. Therefore, the concomitant medication that is highly metabolised in the intestine or has a more narrow therapeutic window may be affected. For example, a DDI could occur with oral contraceptives.

No DDI was observed for bupropion, sodium oxybate and modafinil. Co-administration with olanzapine lead to a decrease in olanzapine exposures by pitolisant. The mechanism is unknown.

2.4.3. Pharmacodynamics

Mechanism of action

Pitolisant is an orally active histamine H3-receptor antagonist/inverse agonist which, via its blockade of histamine auto-receptors enhances the activity of brain histaminergic neurons, a major arousal system with widespread projections to the whole brain. Pitolisant also modulates various neurotransmitter systems, increasing acetylcholine, noradrenaline and dopamine release in the brain.

Primary and Secondary pharmacology

Two new studies were submitted: a receptor occupancy study (P14-08) and an abuse liability study (P16-02).

In P14-08, the receptor occupancy to the H3 receptor was 84% after a single dose of pitolisant HCl 40 mg. The results contribute further to the understanding of the involvement of the H3 receptor in the mechanism of action of pitolisant.

The results from the human abuse liability study (P16-02) showed that drug liking for 40 mg pitolisant and supratherapeutic dose 240 mg pitolisant were similar to placebo. Hence, there is no suggestion that pitolisant has the potential for abuse.

2.4.4. Discussion on clinical pharmacology

Pitolisant displays non-linear pharmacokinetics over the clinical dose range of 5 to 20 mg pitolisant HCl. Since the PK of 5 mg and 10 mg pitolisant has only been investigated in one study using a limited number of subjects, the extrapolation of the exposure-efficacy relationship to the two lower dosages is hampered. The PK of pitolisant at a dose of 20 mg pitolisant HCl was sufficiently investigated in healthy volunteers. Limited PK information is available for the patient population.

The DDI risk of CYP3A inhibitors on the PK of pitolisant in CYP2D6 poor metabolisers is currently unknown and will be investigated post marketing.

2.4.5. Conclusions on clinical pharmacology

The CHMP was of the view that, even though some PK data are limited, the available data are acceptable to support the application.

The study evaluating DDI risk of CYP3A inhibitors on the PK of pitolisant in CYP2D6 poor metabolisers has been requested and will be submitted post marketing.

The relevant PK and PD data are appropriately reflected in the SmPC.

2.5. Clinical efficacy

The clinical development program for pitolisant (also referred to as BF2.649) for the treatment of excessive daytime sleepiness (EDS) in subjects with obstructive sleep apnoea (OSA) comprises two phase 3 studies (HAROSA I and HAROSA II), 3 supportive studies (proof of concept studies P04-01 and P05-01, and dose-finding study P09-16) (see Table 4).

Table 4. Overview of clinical studies

Study ID ***No. Of study centres*** ***Study period*** ***Objective***	***Design*** ***Duration***	***Study Posology*** ***Subjects per arm entered/completed*** ***Study Population***	***Efficacy endpoints***
P04-01 *3 centres* *Sep 2004 – Apr 2005* *Pilot study*	*PC DB* *5 days*	*40 mg (n=12/11)* *no nCPAP*	*Δ number of diurnal sleepiness episodes / total duration of daily diurnal sleepiness*
P05-01 *2 centres* *Aug 2005 – Jan 2007* *Pilot Study*	*PC DB* *14 days*	*40 mg (n=21/10)* *no nCPAP*	*OSleR test*
P09-16 *19 centres* *Oct 2010 – Dec 2011* *Dose Finding Study*	*RD DB PC* *14 days*	*116/115:* *PB (n=24/24)* *5mg (n=23/23)* *10mg (n=24/24)* *20mg (n=23/23)* *40mg (n=22/21)* *nCPAP / no nCPAP*	*Δ ESS score over 14 days between treatment groups*
HAROSA I (P09-08) *35 centres* *Aug 2011 – Mar 2013* *Efficacy/Safety*	*RD DB PC* *12 wks DB + 40 wks OLE*	*244/200:* *PB (n=61)* *pitolisant[B] (n=183)* *nCPAP*	*Δ baseline to end of treatment in ESS score* *ESS Response[1]* *OSleR test*
HAROSA II (P09-09) *29 centres* *Oct 2011 – Jul 2013* *Efficacy/Safety*	*RD DB PC* *12 wks DB + 40 wks OLE*	*268/242* *PB (n=67/61)* *pitolisant[B] (n=201/181)* *no nCPAP*	*Δ baseline to end of treatment in ESS score* *ESS Response[1]* *OSleR test*

Δ= difference score, DB= double blind, ESS= Epworth Sleepiness Scale, nCPAP= nasal Continuous Positive Airway Pressure, OSleR test = Oxford Sleep Resistance test, PB= placebo, PC = placebo controlled, RD= randomized
[A] by clinical assessor
[B] Pitolisant was titrated individually up to maximum tolerance, the maximum daily dose was 20 mg
[1] ESS response was defined by the Applicant as: reaching an absolute value of the ESS inferior to 11 and either reaching an absolute ESS inferior to 11 or an improvement from baseline of at least 3.

2.5.1. Dose response study

Dose response study

Study P09-16 was a double-blind, randomized, placebo-controlled study with pitolisant in adult subjects with moderate to severe OSA experiencing EDS (with an Epworth score ≥ 11).

Two groups of patients were included:

- Group A: patients with OSA having been submitted to nasal Continuous Positive Airway Pressure (nCPAP) therapy for a minimum period of 3 months, and still complaining of Excessive Daytime Sleepiness despite the efforts made beforehand to obtain an efficient nCPAP therapy (normalization of AHI, suppression of respiratory sleep fragmentation);
- Group B: patients with OSA, complaining of Excessive Daytime Sleepiness but refusing to be treated with nCPAP therapy.

The study consisted of a 7- to 14 day washout period, followed by a 14-day double-blind treatment period.

The following doses of treatments were evaluated: 5 mg pitolisant, 10 mg pitolisant, 20 mg pitolisant, 40 mg pitolisant and placebo.

The main efficacy criterion was ESS score change between the treatment's groups during 14 days.

A total of 116 subjects were randomized into the study who were equally distributed between nCPAP or refusing nCPAP groups (n= 58/58). Per dosing group the subjects were divided as followed (nCPAP/refusing nCPAP): placebo (n= 12/12), pitolisant 5 mg (n= 10/13), pitolisant 10 mg (n= 12/12), pitolisant 20 mg (n= 13/10) and pitolisant 20 mg (n= 11/10).

Linear contrast analysis was performed on the adjusted ESS final scores (V3- end of double-blind) of the five treatment groups. This analysis showed that pitolisant decreased daytime sleepiness and that its efficacy statistically significantly increased with the dose (p=0.0003). The result remained statistically significant when taking into account placebo and all pitolisant doses except the highest (p=0.0001) in the model, or placebo and pitolisant 5 mg and 10 mg (p=0.0025). It was not statistically significant with placebo and pitolisant 5 mg alone in the model (p=0.0819).

2.5.2. Main studies

The two main studies, HAROSA-I and HAROSA-II, are virtually identical, with the only difference being the included study population. In HAROSA-I subjects were enrolled who had moderate to severe OCA who experienced residual EDS despite regular nCPAP use. In HAROSA-II subjects with OSA that refused nCPAP therapy were enrolled. An overview of the main selection criteria is presented in Table below.

Table 5. Main selection criteria in OSA studies in adult subjects

	Pilot studies			Pivotal studies	
	P04-01	**P05-01**	**P09-16**	**P09-08 HAROSA I**	**P09-09 HAROSA II**
OSA	Yes	Yes	Yes	Yes	Yes
nCPAP therapy	No	No	Yes or No	Yes	No
AHI	≥20	≥20	≥ 15	≤ 10 under CPAP	≥ 15
PLMAI	-	-	-	≤ 10	≤ 10
ESS score at baseline	≥12	≥12	≥ 11	≥12	≥12
MMSE	-	-	-	≥ 28	≥ 28
BDI	-	-	-	< 16	< 16

AHI=Apnea-Hypopnea Index, BDI= Beck Depression Inventory, ESS= Epworth Sleepiness Scale, MMSE= Mini Mental State Examination, nCPAP= nsal Continuous Positive Airway Pressure, OSA= Obstructive Sleep Apnea, PLMAI= Period Limb Movements Arousal Index,

Due to the main studies being virtually identical with the exception of the in/exclusion criteria, the study design and methods are described for the main studies combined below. The results are presented separately.

HAROSA-I & HAROSA-II

Methods

HAROSA-I and II are phase III, multicentre, randomized, double-blind, placebo-controlled studies in adults with moderate to severe OSA who have residual EDS despite use of nCPAP (HAROSA-I) or refusing nCPAP (HAROSA-II).

The studies consisted of two parts, a 12-week double blind part starting with an escalating dose period, followed by treatment with the selected dose. The second part was the optional open label phase of the study, consisting of a dose escalation phase followed by 40 weeks of treatment. If patients were not willing to continue, they had their end of study visit after a one-week placebo wash-out (V7).

Study Participants

The key inclusion criteria for **HAROSA-I** (with nCPAP) are:

- Patients having been submitted to nCPAP therapy for a minimum period of 3 months and still complaining of Excessive Daytime Sleepiness despite the efforts made beforehand to obtain an efficient nCPAP therapy
- Polysomnography under nCPAP performed between V1 and V2 or during the last 12 months with :
    - Apnoea-Hypopnea Index (AHI) under nCPAP therapy ≤ 10.

    - Periodic limbs movement (PLM) disorders as defined by a PLM arousal index (PLMAI) ≤ 10 per hour.
- nCPAP ≥ 4 hours/day (compliance checked on the clock-time counter of the CPAP machine).

The key inclusion criteria for **HAROSA-II** (without nCPAP) are:

- Patients refusing to be treated by nCPAP therapy, and still complaining of Excessive Daytime Sleepiness.
- Polysomnography performed between V1 and V2 or during the last 12 months with:
    - Apnoea-Hypopnea Index (AHI) ≥15.
    - Periodic Limb Movement Disorders (PLM) as defined by a PLM arousal index (PLMAI) ≤ 10 per hour.

Further an Epworth Sleepiness Score of ≥ 12 was required.

The key exclusion criteria were:

- Patient suffering from chronic severe insomnia according to International Classification of Sleep Disorders (ICSD 2005) without OSA, co-existing narcolepsy (ICSD 2005), sleep debt not due to OSA, or non-respiratory sleep fragmentation
- Any significant serious abnormality of the cardiovascular system, e.g. recent myocardial infarction, angina, hypertension or dysrhythmias (within the previous 6 months), Electrocardiogram Bazett's corrected QT interval higher than 450 ms, history of left ventricular hypertrophy or mitral valve prolapse.
- Patient using prohibited treatments*.

* drugs indicated for somnolence, hypnotic drugs, tricyclic antidepressints, central antihypertensive drugs, psychostimulants, H1 antihistimec products, sodium oxybate, dextropropoxyphene and Surgical intervention including mandibular advancement orthesis and uvulopalatopharyngoplasty (UPPP)

Treatments

Treatment consisted of capsules containing ¼, ½, or one 20 mg tablet of pitolisant or placebo (lactose) were administered by oral route, in the morning, before breakfast.

Dose escalation was performed in the double-blind phase as follows:

- From D1 to D7, pitolisant (or placebo) dose was 5 mg/d.
- From D8 to D14, the dose was 10 mg/d.
- At D15, the dose was increased to 20 mg/d pitolisant (or placebo) if the tolerance was acceptable. If not (i.e. in case of troublesome insomnia), the patient continued taking 10 mg/d or placebo, or the posology could be eventually reduced to 5 mg/d or placebo.
- At D21, the dose was maintained or reduced according to the tolerance, but no dose increase was allowed.

Thereafter, the dose remained stable for a nine-week period (until D84).

The same 3-week dose escalation scheme was used in the first 3 weeks of the open-label phase.

Objectives

The objectives of **HAROSA-I** were:

• To demonstrate the efficacy and safety of pitolisant given at 5, 10, or 20 mg per day versus placebo, during 12 weeks for the double-blind period, for the treatment of excessive diurnal sleepiness in patients with moderate to severe Obstructive Sleep Apnoea (OSA) who experienced residual sleepiness despite regular nasal Continuous Positive Airway Pressure (nCPAP) use.

• To assess the long-term tolerance as well as the maintenance of the efficacy of pitolisant administered at 5, 10, or 20 mg once a day during the 40 weeks open-label phase.

The objectives of **HAROSA-II** were:

• To demonstrate the efficacy and safety of pitolisant given at 5, 10, or 20 mg OD versus placebo, during 12 weeks for the double-blind period, for the treatment of Excessive Daytime Sleepiness (EDS) in patients with moderate to severe Obstructive Sleep Apnoea (OSA) who refused the nasal Continuous Positive Airway Pressure (nCPAP) therapy.

• To assess the long-term tolerance as well as the maintenance of efficacy of pitolisant administered at 5, 10, or 20 mg once a day during the 40 weeks open-label phase.

Outcomes/endpoints

Primary endpoint:

- The change in **Epworth Sleepiness Scale (ESS)** score between baseline (V2) and end of treatment (V6).

Key secondary endpoints:

- **Epworth response**, defined by the Applicant as reaching an absolute value of the ESS inferior to 10 (R1) and either reaching an absolute ESS inferior to 10 or an improvement from baseline of at least 3 (R2).
- **Sleep diaries**. Difference between the treatment groups on Mean Wakefulness duration, Mean Daily Alertness Duration, Mean Daily Number of Sleep Episodes and Mean Daily Duration of Sleep Episodes, during the table treatment period (V5 – V6) corrected for baseline (V2).
- The difference between the treatment groups on the **Oxford Sleep Resistance test (OSleR)** at V6 corrected for baseline (V2)
- The difference between the treatment groups on **Clinical Global Impression change (CGIc)** at V6

Randomisation and blinding (masking)

Randomisation

During the double-blind phase, the investigational treatments were assigned to the eligible patients after the completion of the inclusion visit (V2) and verification of all selection criteria. The study drug (pitolisant or placebo) was allocated to the patients according to a randomization list established on a balanced 3:1 (3 pitolisant for 1 placebo) basis. The randomization of a patient to a treatment group was performed via an electronic Web Randomization Server (Arone eWRS).

Blinding

Two kinds of unitary tablets were manufactured: 20 mg pitolisant HCl tablets and lactose placebo tablets.

The investigational treatments (pitolisant and placebo) were provided as sealed capsules. The capsules were identical in appearance (form, dimension "A", colour, and taste). Each capsule contained either:

- ¼ tablet of pitolisant (i.e. 5mg) or placebo,
- ½ tablet of pitolisant (i.e. 10 mg) or placebo,
- 1 tablet of pitolisant (i.e. 20 mg) or placebo.

Capsules were packaged in blisters containing medication for each treatment week (9 capsules):

- 9 capsules of ¼ tablet of pitolisant (i.e. 5 mg) or 9 capsules of placebo
- 9 capsules of ½ tablet of pitolisant (i.e. 10 mg) or 9 capsules of placebo
- 9 capsules of 1 tablet of pitolisant (i.e. 20 mg) or 9 capsules of placebo

Patients were instructed to take the study treatment with a glass of water when they woke up, every morning before breakfast and to comply with the posology determined by the Investigator according to his own judgment during each period.

For the open-label extension period, patients received bottles containing 30 cross-scored tablets of pitolisant 20 mg and were instructed to take every morning, after waking up and prior to breakfast, ¼, or ½, or 1 tablet of pitolisant 20 mg, with a glass of water, according to the study stage and Investigator's dose regimen prescription based on individual tolerance assessment.

Statistical methods

Efficacy analyses were performed in the Intent-to-Treat (ITT) Population, all randomized patients and based on the treatment to which the patient was randomized. A Per Protocol (PP) population was used as a sensitivity analysis. Safety analyses were performed on the Safety Population (SAF), all patients who received at least one dose of study medication, and for whom at least one valid post-baseline evaluation is available, based on the treatment delivered to the patient.

The primary endpoint, ESS score, will be analysed using an analysis of Covariance (ANCOVA) model, at the two-sided 95% confidence level. It will be conducted using a linear mixed-effects model, considering treatment as a fixed factor, centre as a random factor, and ESS and BMI at V2 as adjustment covariates.

Categorical secondary endpoints will be evaluated using a nonlinear logistic mixed model with treatment as a fixed factor, centre as a random factor, no a-priori centre-treatment interaction, and baseline ESS as the adjustment covariate. Continuous secondary endpoints will be compared by ANCOVA, adjusting for the baseline value and assuming a possible site (centre) main effect. OSleR data are not distributed according to a normal distribution; the geometric mean of the ratios (OSL at V6/OSL at V2) will be compared between the two treatment groups by means of a t-test.

Missing data for the primary efficacy variable and for response will be allocated following the Last Observation Carried Forward (LOCF), defined as the last available assessment at V2, V3, and V4. A sensitivity analysis for the primary efficacy variable will be performed using the baseline value carried forward (BOCF).

All statistical tests were performed two-sided, at the 5% level of significance. No corrections were performed for multiplicity; secondary endpoints were considered as supportive or hypothesis-generating.

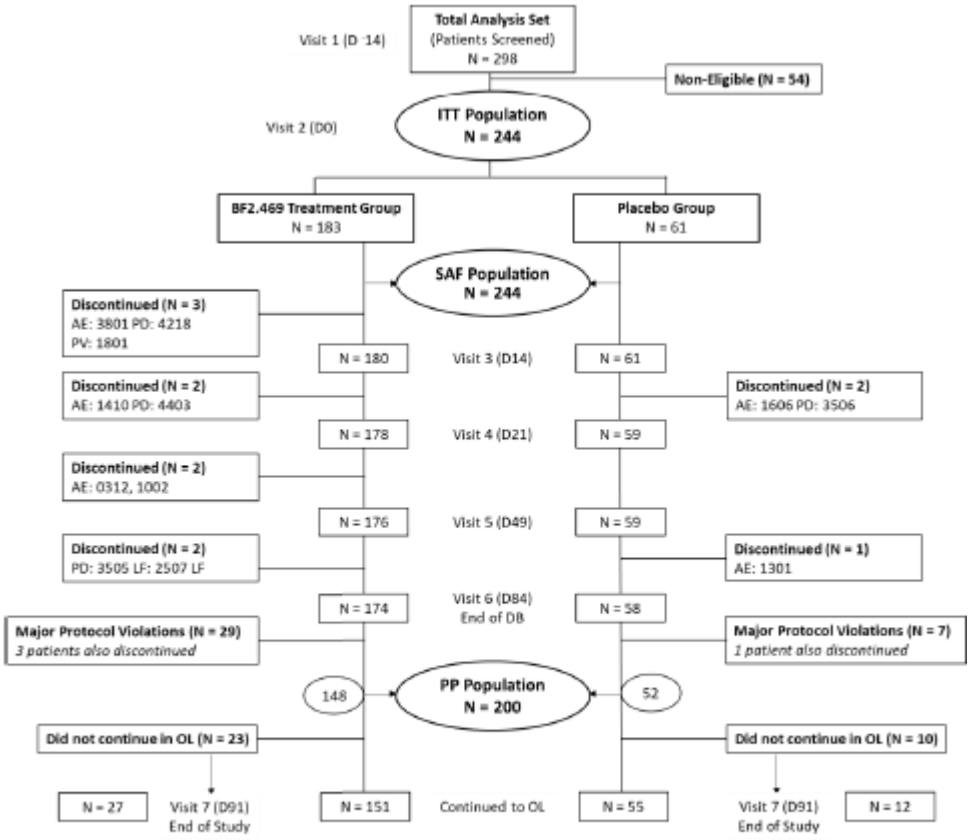
In Harosa I, one futility analysis was performed when 60 patients had terminated the study. In Harosa II, two futility analyses were scheduled (one analysis when 60 patients terminated the study and one analysis when 120 patients terminated the study). These analyses concluded there was no reason to interrupt the trial.

Results – HAROSA-I

Participant flow

The participant flow chart is presented in Figure 3 (double blind) and Figure 4 (open label). A total of 298 subjects were screened, of which 244 were randomized into the study.

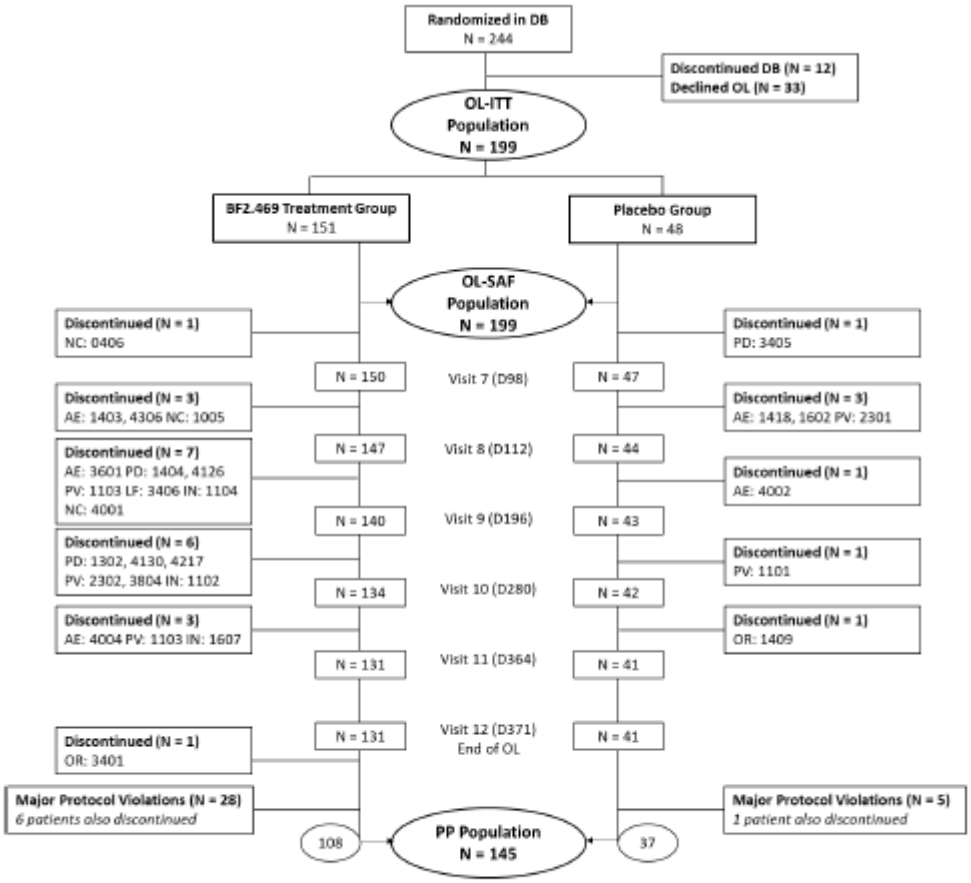
Figure 2. Disposition of Subjects in the Double Blind Phase



ITT = intention to treat; SAF = safety; PP = per protocol; OL = open label
Reasons for discontinuing: AE = adverse event; PD = patient decision; PV = protocol violation

By the end of the titration period (from 5 to 20 mg/daily in pitolisant group), the stable dose was 20 mg for 70.3% of subjects, 10 mg for 21.1% and 5 mg for 8.6% while in the placebo group it was 81.4%, 10.2%, and 8.5%, respectively.

Figure 3. Disposition of Subjects in the Open Label Phase



ITT = intention to treat; SAF = safety; PP = per protocol; OL = open label
Reasons for discontinuing: AE = adverse event; PD = patient decision; PV = protocol violation; NC = not continuing OL; IN = inefficiency; OR = other reason

In the open label phase, in the subjects previously treated with pitolisant, the stable dose was 20 mg for 77.4% of subjects, 10 mg for 17.3% and 5 mg for 5.3% while those previously treated with placebo these were 78.6%, 19.0% and 2.4%, respectively.

Baseline data

The key baseline and demographic characteristics of the double-blind phase are presented in Table 4 below.

Table 6 Baseline data and characteristics in HAROSA-I

Study P09-08	PLACEBO (N=61)	PITOLISANT (N=183)	ALL (N=244)
Age (yr)	51.0 ± 10.6 (25; 72)	53.8 ± 10.5 (23 ; 81)	53.1 ± 10.6 (23; 81)
BMI (kg/m²)	32.17 ±4.28	32.66 ±5.22	-
Gender (Males) % (n)	86.9% (53)	81.4% (149)	82.8% (202)
Time since OSA diagnosis (month)	48.99 ± 57.08 (3.1; 240)	44.84 ± 44.07 (0.2;240.0)	45.89 ± 47.60 (0.2; 240.0)
AHI under nCPAP	4.45 ± 3.07 (0.0; 9.8)	4.08 ± 3.45 (0.0; 28.0)	4.18 ± 3.46 (0.0; 28.0)
Time since residual sleepiness on nCPAP (month)	38.63 ± 45.24 (0.0; 240.0)	35.17 ± 38.48 (-0.2; 240.0)	36.04 ± 40.22 (-0.2; 240.0)
Mean nocturnal SaO_2 (%)	94.29 ± 2.26 (84.0; 98.1)	94.21 ± 2.90 (67.0; 100.0)	94.23 ± 2.75 (67.0; 100.0)
PLMAI ≤ 10/h	2.75 ± 3.22 (0.0; 9.0)	2.36 ± 2.73 (0.0; 9.3)	2.46 ± 2.86 (0.0; 9.3)
Daytime sleep and sleepiness episodes Number Duration (min)	 2.6 ± 1.8 87.6 ± 98.7	 2.7 ± 1.6 83.8 ± 67.3	 2.7 ± 1.7 84.8 ± 76.3
Duration of sleep (hour)	6.95 ± 1.33	7.20 ± 0.99	7.13 ± 1.09
Nocturnal awakening episodes Number Duration (min)	 2.0 ± 2.0 28.8 ± 35.1	 2.3 ± 3.5 27.6 ± 34.5	 2.2 ± 3.2 27.9 ± 34.5
Baseline ESS	14.6 ± 2.8 (12; 22)	14.9 ± 2.7 (8; 23)	-

Numbers analysed

Double blind phase

The intent-to-treat population included 244 subjects:

- 183 subjects in the pitolisant group
- 61 subjects in the placebo group

Open label phase

The intent-to-treat population included 199 subjects:

- 151 subjects rolled over from the pitolisant group
- 48 subjects rolled over from the placebo group

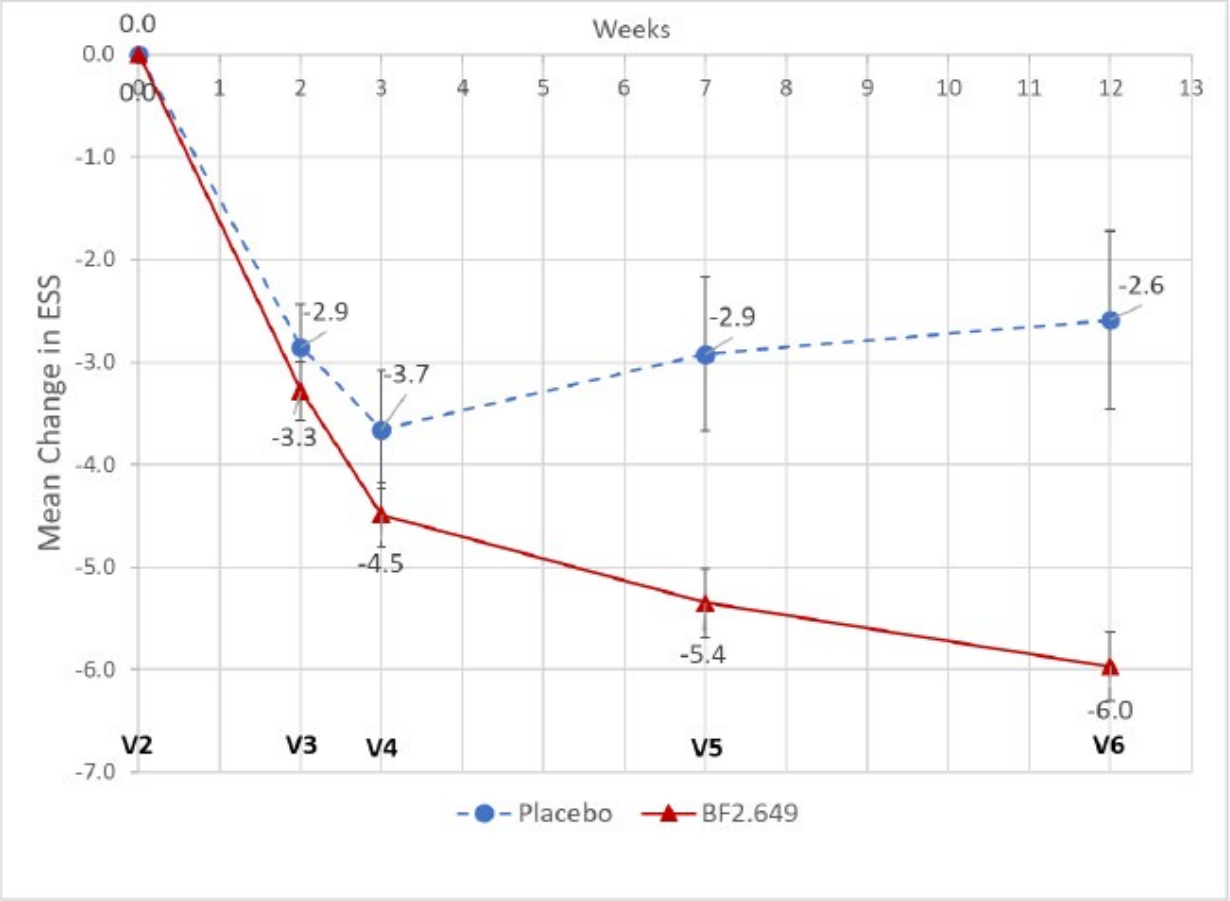
Outcomes and estimation

- Double blind phase

Primary endpoint - ESS

The mean (± SD) ESS scores at baseline (V2) were 14.6 ± 2.8 and 14.9 ± 2.7 in the placebo and pitolisant groups respectively. After 12 weeks of treatment (DB-LOCF ESS), mean ESS score reductions from baseline were -2.75 ± 5.90 in the placebo group and -5.52 ± 4.41 in the pitolisant group (Figure 5).

Figure 4. ESS Mean Change (± SE) in the Double-Blind Phase - ITT Population (N=244)



The mean percentage change in ESS score between V2 and DB-LOCF ESS was -17.33% in the placebo group and -37.0% in the pitolisant treatment group. The final DB-LOCF ESS score was primarily analysed using an ANCOVA model adjusting for ESS and BMI at V2 and study site (centre) as a random effect. There was a statistically significant difference between pitolisant and placebo groups (mean difference: -2.6; 95%CI: -3.9 to -1.4; p<0.001, Table 7).

Table 7. Analysis of DBF-LOCF ESS - ANCOVA (Primary Analysis)

ANCOVA Output	Estimate [95% Confidence Interval]	p-value
Fixed Effect: Treatment		<.001
Fixed Effect: BMI at V2		0.294
Fixed Effect: ESS at V2		<.001
LS Mean BF2.649	9.7 [8.7;10.6]	
LS Mean Placebo	12.3 [11.0;13.6]	
LS Mean (BF2.649 - Placebo)	-2.6 [-3.9;-1.4]	

No multiplicity correction was performed for the analysis of secondary endpoints, therefore the results below are seen as explorative.

ESS response

R1 response (ESS≤10) was observed in 56.3% of the subjects (95% CI: [48.8% - 63.6%]) in the pitolisant group, and 42.6% (95% CI: [30.0% - 55.9%]) in the placebo group (see Table 12). R2 response (ESS≤10 or improvement ≥3) was observed in 71.0% of the subjects (95% CI: [63.9% - 77.5%]) in the pitolisant group and 54.1% (95% CI: [40.8% - 66.9%]) in the placebo group (see **Error! Reference source not found.**). A statistically significant treatment effect was shown for R1 and R2 response (nominal p=0.028 and 0.013 respectively).

Table 8. Response (R1 and R2) - Frequency Distribution and Exact 95% Confidence Interval

Variable	Responder	BF2.649 (N = 183) n % CI	Placebo (N = 61) n % CI
R1	No	80 (43.7% [36.4%; 51.2%])	35 (57.4% [44.1%; 70.0%])
	Yes	103 (56.3% [48.8%; 63.6%])	26 (42.6% [30.0%; 55.9%])
R2	No	53 (29.0% [22.5%; 36.1%])	28 (45.9% [33.1%; 59.2%])
	Yes	130 (71.0% [63.9%; 77.5%])	33 (54.1% [40.8%; 66.9%])

R1 = DBF-LOCF ESS <= 10 (yes, no)
R2 = [(DBF-LOCF ESS <= 10) or (DBF-LOCF ESS <= ESS at V2 - 3)] (yes, no)
Final ESS (DBF) is the average of the non-missing values at V5 and V6. If both values are missing the following imputation is used:
DBF-LOCF ESS (last observation carried forward) = last available ESS at V2, V3, and V4
Reference listing: 16.2.6.1

Sleep diaries

Table 7 displays the difference between the baseline measurement (V1-V2) and the stable treatment period (V5-V6) for the sleep diary variables analysed.

Table 9. Difference between Mean Wakefulness duration, Mean Daily Alertness Duration, Mean Daily Number of Sleep Episodes and Mean Daily duration of Sleep Episodes at Baseline Period (V1-V2) and Stable Treatment Period (V5-V6)

Variable		BF2.649 (N = 183)	Placebo (N = 61)
Mean wakefulness duration (h)	Mean	0.04	0.14
	95% CI on the mean	[-0.18; 0.26]	[-0.14; 0.42]
	Std Dev	1.19	0.90
	Minimum	-4.9	-2.4
	1st quartile	-0.46	-0.54
	Median	0.00	0.08
	3rd quartile	0.75	0.71
	Maximum	3.0	2.5
	n	116	42
	Missing	67	19
Mean daily alertness duration (h)	Mean	0.89	0.93
	95% CI on the mean	[0.60; 1.19]	[0.44; 1.42]
	Std Dev	1.58	1.57
	Minimum	-4.1	-2.1
	1st quartile	0.08	-0.17
	Median	0.85	1.02
	3rd quartile	1.67	2.00
	Maximum	7.1	5.3
	n	112	42
	Missing	71	19
Mean daily number of sleep episodes	Mean	-2.09	-1.34
	95% CI on the mean	[-2.42; -1.77]	[-1.85; -0.84]
	Std Dev	1.78	1.67
	Minimum	-10.0	-5.3
	1st quartile	-3.33	-2.33
	Median	-2.00	-1.17
	3rd quartile	-1.00	-0.33
	Maximum	2.0	3.0
	n	120	44
	Missing	63	17

Variable		BF2.649 (N = 183)	Placebo (N = 61)
Mean daily duration of sleep episodes (min)	Mean	-51.78	-47.66
	95% CI on the mean	[-64.35; -39.21]	[-68.01; -27.30]
	Std Dev	69.25	66.95
	Minimum	-323.3	-318.3
	1st quartile	-76.67	-80.00
	Median	-45.00	-39.17
	3rd quartile	-20.00	-6.67
	Maximum	300.0	90.0
	n	119	44
	Missing	64	17

Only diary cards from first 3 days are used in calculations.

Times in bed between 00:00 and 04:00 are interpreted as midnight hours (+24h). Times in bed between 04:00 and 13:00 are interpreted as evening hours (+12h).

The analyses of mean wakefulness duration (SDWD), mean daily alertness duration (SDAD), mean daily number of sleep/sleepiness episodes (SDNS), and daily duration of sleep/sleepiness episodes (SDDS) during the stable treatment period showed no statistically significant difference between the two treatment groups (p=0.994, p=0.794, p=0.060, and p=0.695, respectively).

OSleR

The geometric mean of sleep latency (OSL) was 15.53 minutes at V2 and 22.31 minutes at V6 in the pitolisant treatment group. In the placebo group, it was 18.99 minutes at V2 and 21.94 minutes at V6. The geometric mean of the ratio was 1.44 in the pitolisant treatment group and 1.22 in the placebo group. The geometric mean of the ratios was not statistically significantly different in the two treatment groups (t-test, nominal p=0.075).

Table 10. Osler Test – ITT Population (N=244)

	BF2.649 (N=183)		Placebo (N=61)	
Variable	V2	V6	V2	V6
OSL (min)				
Geometric Mean	15.53	22.31	18.99	21.94
Range	0.3 to 40.0	1.3 to 40.0	0.7 to 40.0	0.7 to 40.0
N	178	168	60	56
OSL V6 / OSL V2				
Geometric Mean	1.442		1.219	
Range	0.30 to 13.25		0.29 to 4.29	
N	167		56	
Normal Vigilance				
N (%)	6 (3.5%)	26 (15.6%)	3 (5.1%)	8 (14.5%)
95% CI	1.3% - 7.4%	10.4% - 22.0%	1.1% - 14.1%	6.5% - 26.7%

Source: Statistical Tables 14.2.1.2.3.1-DB, 14.2.1.2.3.2-DB and 14.2.1.2.3.4-DB
OSL = Osler sleep latency

CGIc

In the pitolisant treatment group, 78.0% of the subjects were assessed as improved at V6 (Table 9). In this group, subjects were assessed as follows: 11.0% very much improved, 42.2% much improved, and 24.9% minimally improved, 19.1% no change was assessed, and 2.9% minimally worse.

In the placebo group, 53.4% of the subjects were assessed as improved at V6 (Table 9). In this group subjects were assessed as follows: 6.9% very much improved, 27.6% much improved, and 19.0% minimally improved, 31.0% no change, 13.8% minimally worse and 1.7% much worse.

The analysis of CGI-C improvement at V6 using logistic regression showed a statistically significant difference between the two treatment groups (nominal p<0.001).

table 11. Clinical Global Impression of Improvement at V6 and V7

			BF2.649 (N = 183)		Placebo (N = 61)	
Variable	Visit	Improvement	n	% CI	n	% CI
Clinical Global Impression of Improvement	Visit V6	Improved	135	(78.0% [71.1%; 84.0%])	31	(53.4% [39.9%; 66.7%])
		Not improved	38	(22.0% [16.0%; 28.9%])	27	(46.6% [33.3%; 60.1%])
	Visit V7	Improved	15	(57.7% [36.9%; 76.6%])	3	(25.0% [5.5%; 57.2%])
		Not improved	11	(42.3% [23.4%; 63.1%])	9	(75.0% [42.8%; 94.5%])

Clinical Global Impression of Improvement:
Improved = Very much improved, much improved, or minimally improved
Not improved = No change, minimally worse, much worse, or very much worse
At Visit V7 only patients who do not continue in the open label part of the study are considered in the analysis.

PGOE

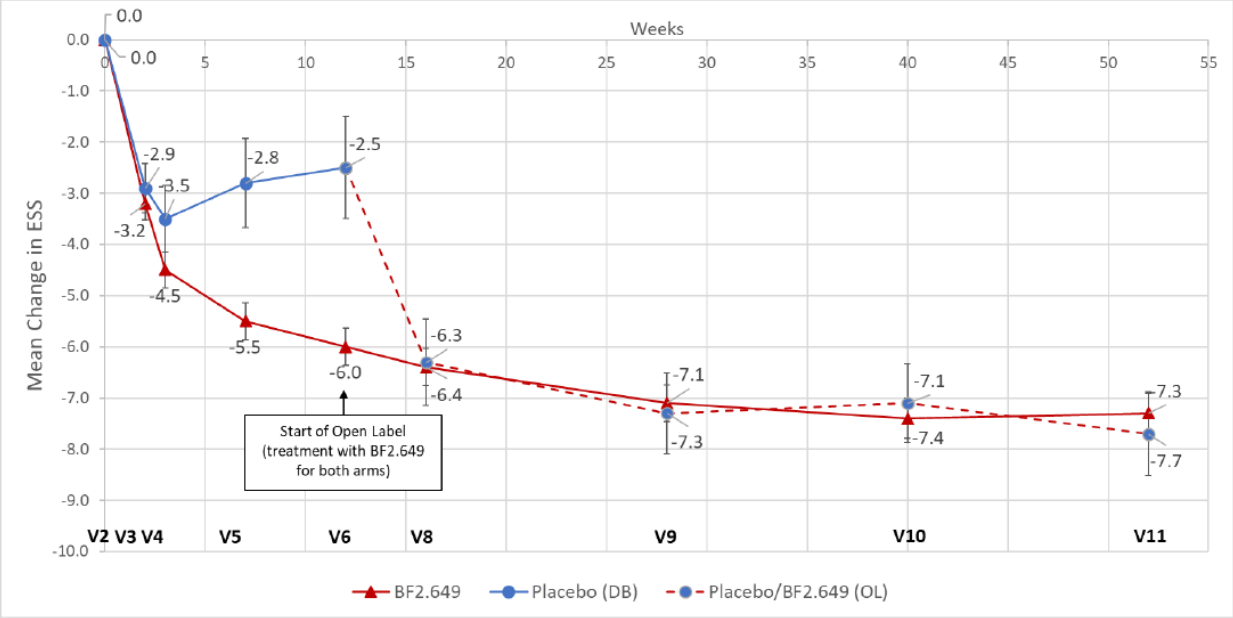
PGOE improvement was observed in the pitolisant treatment group at V6 for 76.4% of the subjects (marked effect 33.3%, moderate effect 27.6%, minimal effect 15.5%). In the placebo group, PGOE improvement was observed at V6 in 56.9% of the subjects (marked effect 25.9%, moderate effect 10.3%, minimal effect 20.7%). The analysis of PGOE improvement at V6 by means of logistic regression showed a statistically significant difference between the two treatment groups (nominal p=0.005).

Open-label phase

At open-label baseline (V5/V6), the average ESS (±SD) was 12.0 ± 6.0 and 9.4 ± 4.8, respectively. The mean change in ESS score between V2, and open-label baseline was -2.65 ± 6.25 in subjects treated with placebo in the double-blind phase and -5.76 ± 4.38 in the subjects treated with pitolisant during the double-blind phase of the study.

After 40 weeks of treatment, mean ESS score reductions from open-label baseline were -4.07 ± 5.29 in subjects treated with placebo in the double-blind phase and -1.21 ± 3.12 in the subjects treated with pitolisant during the double-blind phase of the study. For the subjects treated with pitolisant during the double-blind phase of the study, the primary model showed a mean decrease of -1.2 (95%CI: [-1.7;-0.7. For the subjects treated with placebo during the double-blind phase of the study, the primary model showed a mean decrease of -3.2 (95%CI: [-5.0;-1.4]).

Figure 5. Mean ESS Change in ESS Score – OL-ITT Population



ESS response

At the end of the open label phase, R1 response (ESS≤10) was 68.9% (95% CI: [60.8% - 76.2%]) in the subjects treated with pitolisant during the double-blind phase, and 75.0% (95% CI: [60.4% - 86.4%]) in subjects treated with placebo during the double-blind phase. R2 response (ESS≤10 or improvement ≥ 3) was 82.1% (95% CI: [75.1% - 87.9%]) in the subjects treated with pitolisant during the double-blind phase and 77.1% (95% CI: [62.7% - 88.0%]) in subjects treated with placebo.

Ancillary analyses

The final DBF-BOCF ESS score was analysed using the same ANCOVA model as for the primary analysis on the ESS. For the ITT Population this analysis also showed a statistically significant treatment effect ($p<0.001$). Two models making use of DBF-LOCF but without controlling for BMI at V2 and for neither BMI and ESS at V2 also showed a statistically significant treatment effect (nominal $p<0.001$).

No subgroup analyses or exposure-response analyses were performed.

Summary of main efficacy results

The following tables summarise the efficacy results from the main study HAROSA-1 supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table 12. Summary of efficacy for trial HAROSA-I

Title: BF2.649 in patients with Obstructive Sleep Apnoea syndrome (OSA), and treated by nasal Continuous Positive Airway Pressure (nCPAP), but still complaining of Excessive Daytime Sleepiness (EDS)			
Study identifier	P09-08 (HAROSA-I) EudraCT No: 2009-017348-14		
Design	Randomized, double-blind, placebo-controlled, parallel group, multicentre, fixed dose study		
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:		12 weeks 2 weeks [illegible]
Hypothesis	Superiority of pitolisant vs. placebo		
Treatments groups	Pitolisant*		Pitolisant 12 weeks
	Placebo		Placebo 12 weeks
Endpoints and definitions	Primary endpoint	ESS	Change in Epworth Sleepiness Scale Score (ESS) between baseline (V2) and end of treatment (V6)
	Secondary endpoints	ESS responder	R1: reaching an absolute value of the ESS inferior to 11 R2: either reaching an absolute ESS inferior to 11 or an improvement from baseline of at least [illegible]
		Sleep diaries	Difference between the treatment groups on Mean Wakefulness duration, Mean Daily Alertness Duration, Mean Daily Number of Sleep Episodes and Mean Daily Duration of Sleep Episodes, during the table treatment period (V5 – V6) corrected for baseline (V2).

		OSleR	Difference between the treatment groups on the Oxford Sleep Resistance test (OSleR) at V6 corrected for baseline (V2)
		CGI-C	Difference between the treatment groups on Clinical Global Impression change (CGI) at V6
		PGOE	Difference between the treatment groups on Patient's Global Opinion on Efficacy (PGOE) compared to pre-study conditions
Database lock	26/03/2015		

Results and Analysis

Analysis description	**Primary Analysis**		
Analysis population and time point description	Intent to treat V6 – end of double blind		
Descriptive statistics and estimate variability	Treatment group	**Placebo**	**Pitolisant**
	Number of subject	61	183
	ESS	-2.75	-5.52
	SD	5.90	4.41
	ESS Response	R1: 42.6% R2: 54.1%	R1: 56.3% R2: 71.0%
	95% CI	R1: 30.0% ;55.9% R2: 40.8% - 66.9%	R1: 48.8% ; 63.6% R2: 63.9% ; 77.5%
	Sleep diaries Mean difference	SDWD: 0.14 SDAD: 0.93 SDNS: -1.34	SDWD: 0.04 SDAD: 0.89 SDNS: -2.09
	SD	SDWD: 0.90 SDAD: 1.57 SDNS: 1.57	SDWD: 1.19 SDAD: 1.58 SDNS: 1.78
	OSleR Geometric mean	1.219	1.442
	Range	0.29 – 4.29	0.30 – 13.25
	CGIc	53.4%	78.0%
	95% CI	39.9; 66.7	71.1 ; 84.0

	PGOE		
	95% CI	43.2% - 69.8%	69.4% - 82.5%
Effect estimate per comparison	Primary endpoint **ESS**	Comparison groups	**Placebo | Pitolisant**
		LSM mean difference	-2.6
		95% CI	-3.9 ; -1.4
		P-value	*p<0.001*
	ESS response	Comparison groups	**Placebo | Pitolisant**
		Responder %	R1: 42.6% | 56.3% R2: 54.1% | 71.0%
		95% CI	R1: 30.0% ; 55.9% | 48.8% ; 63.6% R2: 40.8% - 66.9% | 63.9% ;
		Nominal P-value *(Nonlinear logistic mixed*	*R1 p=0.028* *R2 p=0.013*
	Sleep diaries	Comparison groups	**Placebo | Pitolisant**
		LSMean difference SDWD SDAD	 -0.0 -0.1
		95%CI SDWD SDAD	 0.3; 0.3 -0.5; 0.4
		Nominal P-value *SDWD* *SDAD* *SDNS*	*p=0.994* *p= 0.794* *p= 0.060* *p= 0.695*
	OSIeR	Comparison groups	**Placebo | Pitolisant**
		Geometric mean difference	1.219 | 1.442
		Range	0.29 – 4.29 | 0.30 – 13.25
		Nominal P-value	*p=0.075*
	CGI	Comparison groups	**Placebo | Pitolisant**
		% Improved	53.4% | 78.0%
		95% CI	39.9% - 66.7% | 71.1% - 84.0%
		Nominal P-value *(Nonlinear logistic mixed*	*p<0.001*

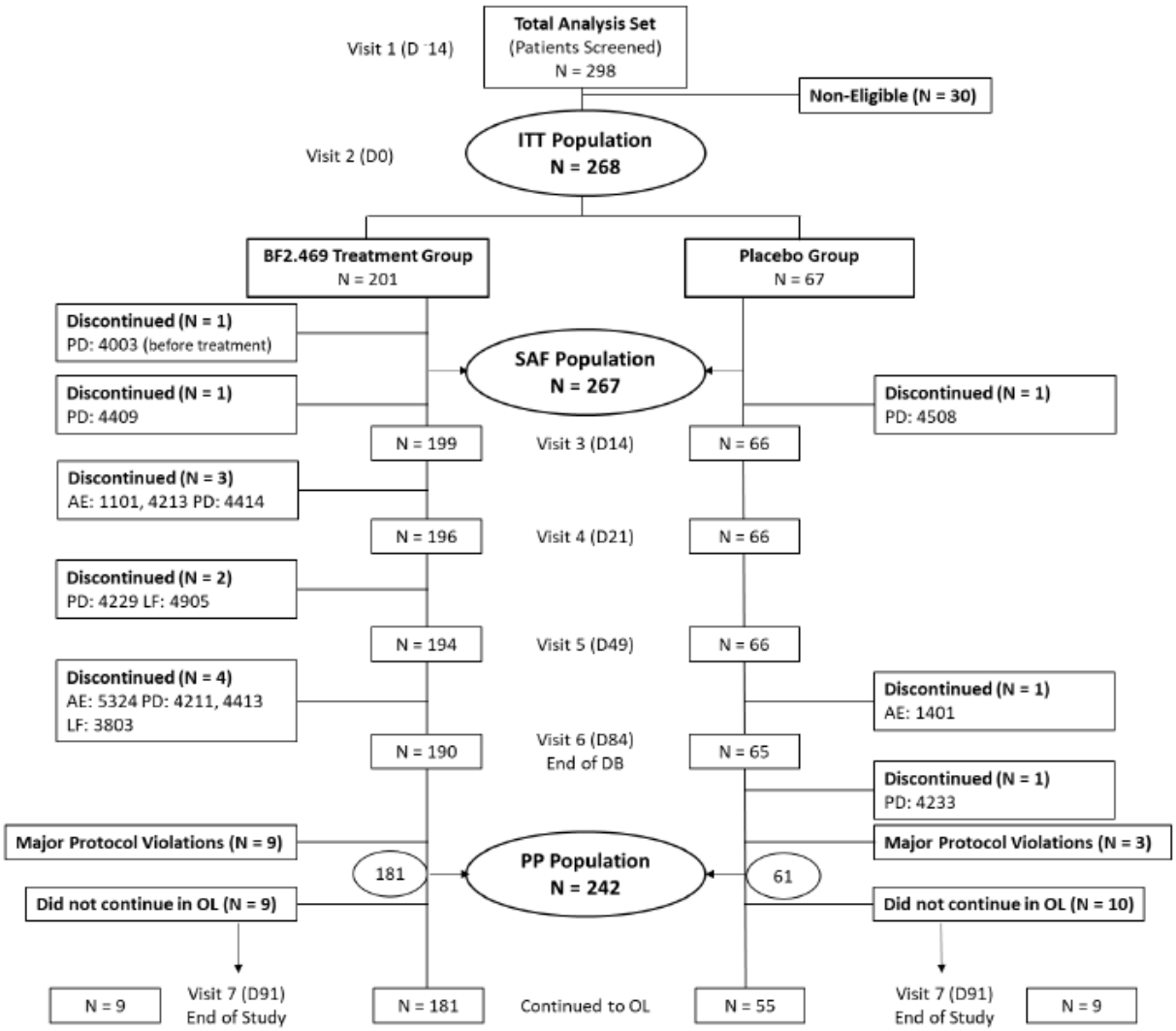
	PGOE	Comparison groups	**Placebo | Pitolisant**
		% Improved	*56.9% | 76.4%*
		95%CI	43.2% - 69.8% | 69.4% - 82.5%
		Nominal P-value	*p=0.005*
Notes	*By the end of the titration period (from 5 to 20 mg/daily in pitolisant group), the stable dose was 20 mg for 70.3% of patients, 10 mg for 21.1% and 5 mg for 8.6% while in the placebo group it was 81.4%, 10.2%, and 8.5%,		

Results – HAROSA-II

Participant flow

The participant flow chart is presented in Figure 7 (double-blind) and Figure 8 (open-label). A total of 298 subjects were screened of which 268 were randomized into the study.

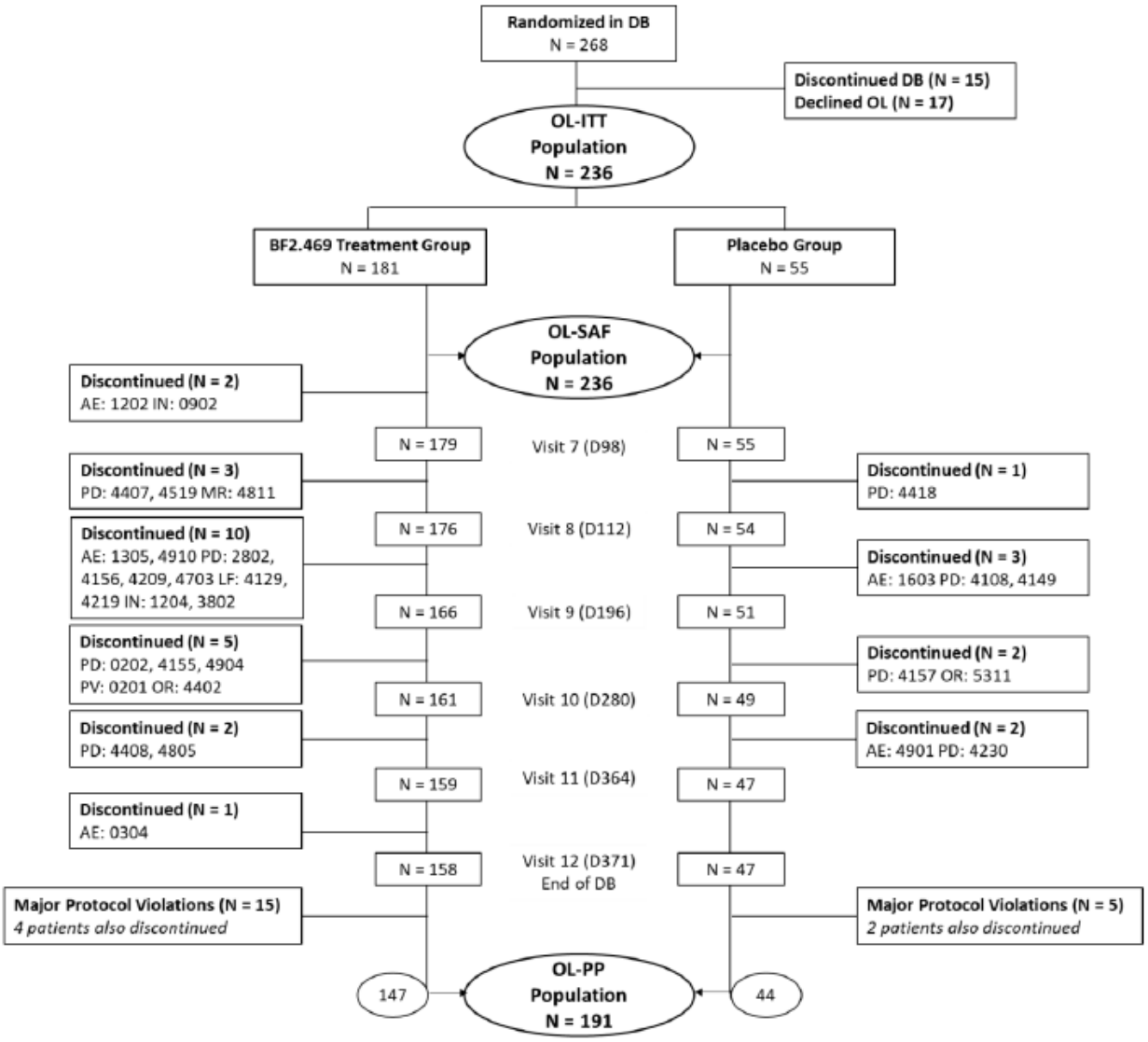
Figure 6. Disposition of Subjects in the Double-Blind Phase



ITT = intention to treat; SAF = safety; PP = per protocol; OL = open label
Reasons for discontinuing: AE = adverse event; PD = patient decision; LF = lost to follow-up

By the end of the titration period (from 5 to 20 mg/daily in pitolisant group), the stable dose was 20 mg for 75.4% of subjects, 10 mg for 15.7% and 5 mg for 8.9% while in the placebo group these were 81.5%, 10.8%, and 7.7%, respectively.

Figure 7. Disposition of Subjects in the Open Label Phase



ITT = intention to treat; SAF = safety; PP = per protocol; OL = open label
Reasons for discontinuing: AE = adverse event; PD = patient decision; PV = protocol violation; LF = lost to follow-up; IN = inefficiency; MR = medical reason; OR = other reason

In the open-label phase, in the subjects previously treated with pitolisant, the stable dose was 20 mg for 76.3% of subjects, 10 mg for 12.2% and 5 mg for 11.5%, while those previously treated with placebo these were 78.3%, 15.2% and 6.5%, respectively

Baseline data

The key baseline and demographic characteristics for the double-blind period are presented in Table 9 below.

Table 13. Baseline data and characteristics in HAROSA-I

Study P09-09	PLACEBO (N=67)	PITOLISANT (N=201)	ALL (N=268)
Age (yr)	52.1 ± 11.0 (30; 76)	51.9 ± 10.6 (25; 75)	52.0 ± 10.6 (25; 76)
BMI (kg/m²)	33.0±4.3	32.8±4.6	-
Gender (Males) % (n)	76.1% (51)	75.1% (151)	75.4% (202)
Time since OSA diagnosis (month)	11.5 ± 23.2 (-0.2; 154.5)	12.1 ± 25.0 (-0.5;228.0)	11.9 ± 24.5 (-0.5; 228.0)
AHI at date of diagnosis	46.9 ± 22.8 (15.4; 103.5)	50.2 ± 44.3 (15.0; 568.0)	49.3 ± 40.0 (15.0; 568.0)
Mean nocturnal SaO_2 (%)	90.9 ± 3.8 (74; 96)	89.8 ± 9.1 (6; 97)	90.1 ± 8.2 (6; 97)
Daytime sleep and sleepiness episodes Number Duration (min)	 3.2 ± 1.9 82.9 ± 59.6	 3.5 ± 1.9 87.8 ± 63.1	 3.5 ± 1.9 86.6 ± 62.2
Duration of sleep (hour)	7.09 ± 0.95	7.27 ± 1.11	7.22 ± 1.08
Nocturnal awakening episodes Number Duration (min)	 2.2 ± 1.1 38.6 ± 33.9	 2.5 ± 2.0 37.9 ± 42.4	 2.4 ± 1.8 38.1 ± 40.4
Baseline ESS	15.7 ± 3.6 (10; 24)	15.7 ± 3.1 (7; 24)	-

Numbers analysed

Double blind phase

The intent-to-treat population included 268 subjects:

- 201 subjects in the pitolisant group
- 67 subjects in the placebo group

Open label phase

The intent-to-treat population included 236 subjects:

- 181 subjects rolled over from the pitolisant group
- 55 subjects rolled over from the placebo group

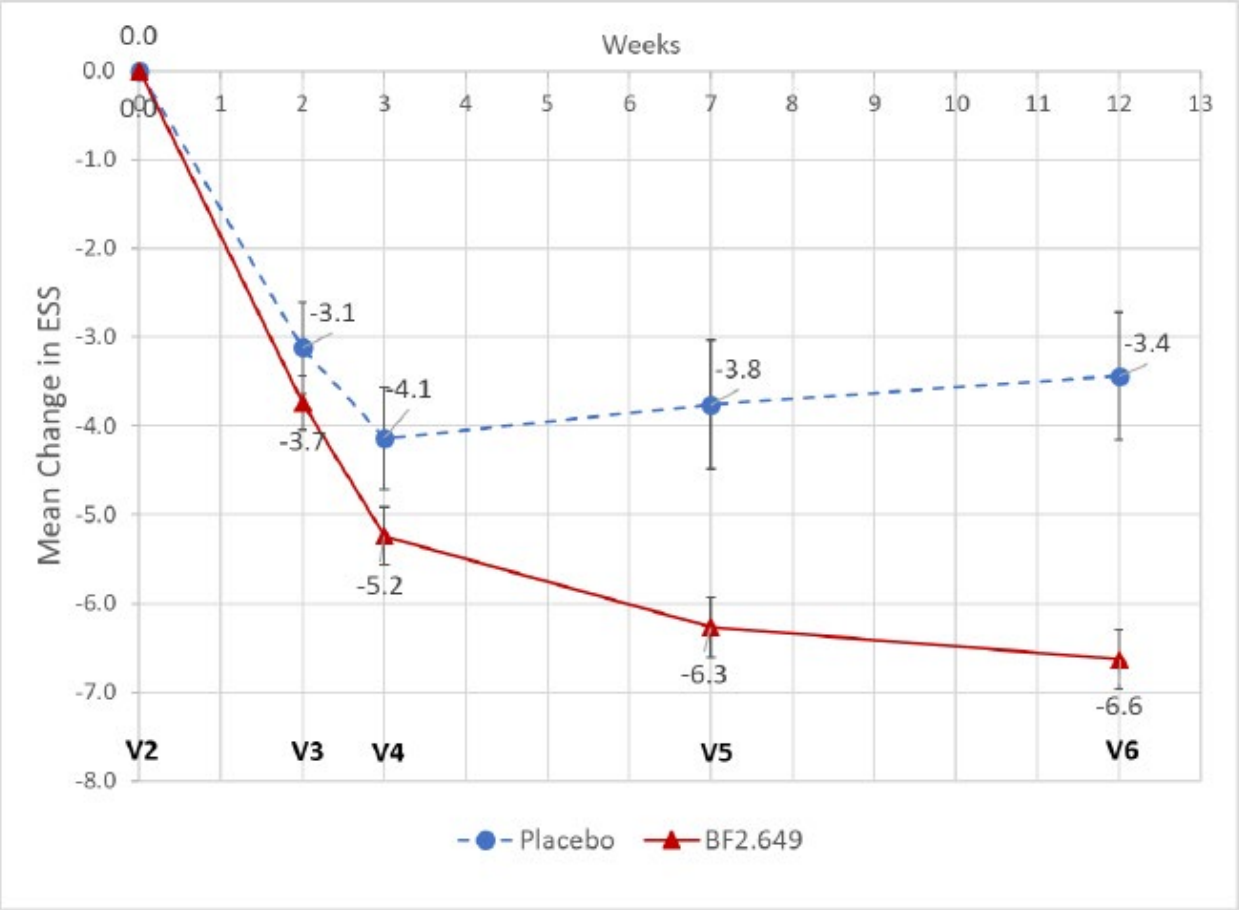
Outcomes and estimation

Double-blind phase

ESS- primary endpoint

The mean (± SD) ESS scores at baseline (V2) were 15.7 ± 3.6 and 15.7± 3.1 in the placebo and pitolisant groups, respectively. After 12 weeks of treatment (DBF-LOCF ESS), mean ESS score reductions from baseline were -3.6 ± 5.5 in the placebo group and -6.3 ± 4.5 in the pitolisant group (**Error! Reference source not found.**).

Figure 8. ESS Mean Change (± SE) in the Double-Blind Phase - ITT Population (N= 268)



The mean percentage change in ESS score between V2 and DBF-LOCF ESS was -22.1 ± 35.4% in the placebo group and -39.7 ± 26.6% in the pitolisant treatment group

The final DBF-LOCF ESS score was primarily analyzed using an ANCOVA model adjusting for ESS and BMI at V2 and study site (centre) as a random effect (see Table 11). For the ITT Population this model showed a statistically significant treatment effect of -2.8 (95% CI: [-4.0;-1.5]) (p<0.001).

Table 14. Analysis of DBF-LOCF ESS - ANCOVA (Primary Analysis)

ANCOVA Output	Estimate [95% Confidence Interval]	p-value
Fixed Effect: Treatment		<.001
Fixed Effect: BMI at V2		0.817
Fixed Effect: ESS at V2		<.001
LS Mean BF2.649	9.8 [8.8;10.7]	
LS Mean Placebo	12.5 [11.2;13.8]	
LS Mean (BF2.649 - Placebo)	-2.8 [-4.0;-1.5]	

No multiplicity correction was performed for the analysis of secondary endpoints, therefore the results below are seen as explorative

ESS Response

Epworth response was defined by the Applicant as reaching an absolute value of the ESS inferior to 10 (R1) and either reaching an absolute ESS inferior to 10 or an improvement from baseline of at least 3 (R2).

R1 response (ESS≤10) was observed in 67.2% of the subjects (95% CI: [60.2% ; 73.6%]) in the pitolisant treatment group, and 44.8% (95% CI: [32.6% ; 57.4%]) in the placebo group (Table 12). R2 response (ESS≤10 or improvement ≥3) was observed in 80.6% of the subjects (95% CI: [74.4% ; 85.8%]) in the pitolisant treatment group and 53.7% (95% CI: [41.1% ; 66.0%]) in the placebo group (Table 12). For both R1 and R2 this model showed a statistically significant treatment effect (nominal p<0.001 for both definitions of response).

Table 15. Response (R1 and R2) - Frequency Distribution and Exact 95% Confidence Interval

		BF2.649 (N = 201)			Placebo (N = 67)		
Variable	Responder	n	%	CI	n	%	CI
R1	No	66	32.8%	[26.4%; 39.8%]	37	55.2%	[42.6%; 67.4%]
	Yes	135	67.2%	[60.2%; 73.6%]	30	44.8%	[32.6%; 57.4%]
R2	No	39	19.4%	[14.2%; 25.6%]	31	46.3%	[34.0%; 58.9%]
	Yes	162	80.6%	[74.4%; 85.8%]	36	53.7%	[41.1%; 66.0%]

R1 = DBF-LOCF ESS <= 10 (yes, no)
R2 = [(DBF-LOCF ESS <= 10) or (DBF-LOCF ESS <= ESS at V2 - 3)] (yes, no)
Final ESS (DBF) is the average of the non-missing values at V5 and V6. If both values are missing the following imputation is used:
DBF-LOCF ESS (last observation carried forward) = last available ESS at V2, V3, and V4

Sleep diaries

Table 13 displays the difference between the baseline measurement (V1-V2) and the stable treatment period (V5-V6) for the sleep diary variables analysed.

Table 16. Difference between Mean Wakefulness duration, Mean Daily Alertness Duration, Mean Daily Number of Sleep Episodes and Mean Daily duration of Sleep Episodes at Baseline Period (V1-V2) and Stable Treatment Period (V5-V6)

Variable		BF2.649 (N = 201)	Placebo (N = 67)
Mean wakefulness duration (h)	Mean	0.22	0.21
	95% CI on the mean	[0.05; 0.39]	[-0.06; 0.48]
	Std Dev	1.12	1.04
	Minimum	-3.2	-1.5
	1st quartile	-0.33	-0.46
	Median	0.22	0.02
	3rd quartile	0.83	0.67
	Maximum	4.6	4.1
	n	166	59
	Missing	35	8
Mean daily alertness duration (h)	Mean	1.01	0.87
	95% CI on the mean	[0.79; 1.23]	[0.50; 1.24]
	Std Dev	1.44	1.42
	Minimum	-2.9	-1.7
	1st quartile	0.25	-0.19
	Median	0.96	0.58
	3rd quartile	1.83	1.79
	Maximum	5.0	4.5
	n	165	59
	Missing	36	8
Mean daily number of sleep episodes	Mean	-1.79	-1.30
	95% CI on the mean	[-2.09; -1.49]	[-1.78; -0.82]
	Std Dev	1.97	1.86
	Minimum	-13.3	-7.0
	1st quartile	-2.67	-2.33
	Median	-1.67	-1.00
	3rd quartile	-0.67	-0.67
	Maximum	6.0	7.0
	n	171	60
	Missing	30	7

Variable		BF2.649 (N = 201)	Placebo (N = 67)
Mean daily duration of sleep episodes (min)	Mean	-47.87	-32.24
	95% CI on the mean	[-55.95; -39.78]	[-44.85; -19.63]
	Std Dev	53.39	48.82
	Minimum	-240.0	-156.7
	1st quartile	-71.00	-55.00
	Median	-42.50	-28.33
	3rd quartile	-15.00	-3.33
	Maximum	110.0	70.0
	n	170	60
	Missing	31	7

Only diary cards from first 3 days are used in calculations.
Times in bed between 00:00 and 04:00 are interpreted as midnight hours (+24h). Times in bed between 04:00 and 13:00 are interpreted as evening hours (+12h).
Subject 3903 has sleep diary data at Visit7-Visit8 which is not taken into account.

The analyses of mean wakefulness duration, mean daily alertness duration, mean daily number of sleep/sleepiness episodes, and mean daily duration of sleep/sleepiness episodes during the stable treatment period showed no statistically significant difference between the two treatment groups (the nominal p-values are p=0.510, p=0.905, p=0.056, and p=0.066, respectively).

OSleR

The geometric mean of sleep latency (OSL) was 9.94 min at V2 and 16.22 min at V6 in the pitolisant treatment group. In the placebo group, it was 10.88 min at V2 and 14.56 min at V6. The geometric mean of the ratio was 1.65 in the pitolisant treatment group and 1.39 in the placebo group. The geometric mean of the ratios was not statistically significantly different in the two treatment groups (t-test: nominal p=0.167).

Table 17 Osler Test – ITT Population (N=268)

	BF2.649 (N=201)		Placebo (N=67)	
Variable	V2	V6	V2	V6
OSL (min)				
Geometric Mean	9.94	16.22	10.88	14.56
Range	0.2 to 40.0	0.7 to 44.7	0.2 to 40.0	0.7 to 40.0
N	200	189	67	64
OSL V6 / OSL V2				
Geometric Mean	1.65		1.39	
Range	0.17 to 29.0		0.22 to 34.0	
N	188		64	
Normal Vigilance				
N (%)	4 (2.0%)	16 (8.5%)	2 (3.0%)	4 (6.3%)
95% CI	0.5% - 5.0%	4.9% - 13.5%	0.4% - 10.4%	1.7% - 15.2%

Source: Statistical Tables 14.2.1.2.3.1-DB, 14.2.1.2.3.2-DB and 14.2.1.2.3.4-DB

CGIc

In the pitolisant treatment group, 84.2% of the subjects were assessed as improved at V6 (Table 15). In this group, subjects were assessed as follows: 11.1% very much improved, 44.2% much improved, and 28.9% minimally improved, 15.8% no change was assessed and 0% minimally worse.

In the placebo group, 56.3% of the subjects were assessed as improved at V6 (Table 15). In this group, subjects were assessed as follows: 4.7% very much improved, 29.9% much improved, and 21.9% minimally improved, 34.4% no change, and 9.4% minimally worse.

The analysis of CGI-C improvement at V6 using logistic regression showed a statistically significant difference between the two groups (nominal p<0.001).

Table 18 Clinical Global Impression of Improvement at V6 and V7

			BF2.649 (N = 201)			Placebo (N = 67)		
Variable	Visit	Improvement	n	%	CI	n	%	CI
Clinical Global Impression of Improvement	Visit V6	Improved	160	84.2%	[78.2%; 89.1%]	36	56.3%	[43.3%; 68.6%]
		Not improved	30	15.8%	[10.9%; 21.8%]	28	43.8%	[31.4%; 56.7%]
	Visit V7	Improved	5	55.6%	[21.2%; 86.3%]	4	44.4%	[13.7%; 78.8%]
		Not improved	4	44.4%	[13.7%; 78.8%]	5	55.6%	[21.2%; 86.3%]

Clinical Global Impression of Improvement:
Improved = Very much improved, much improved, or minimally improved
Not improved = No change, minimally worse, much worse, or very much worse
At Visit V7 only patients who do not continue in the open label part of the study are considered in the analysis.

PGOE

PGOE improvement was observed in the pitolisant treatment group at V6 for 86.3% of the subjects (marked effect 30.0%, moderate effect 33.7%, minimal effect 22.6%). In the placebo group, PGOE improvement was observed at V6 in 60.9% of the subjects (marked effect 21.9%, moderate effect 18.8%, minimal effect 20.3%). The analysis of PGOE improvement at V6 using logistic regression showed a statistically significant difference between the two treatment groups (nominal p<0.001).

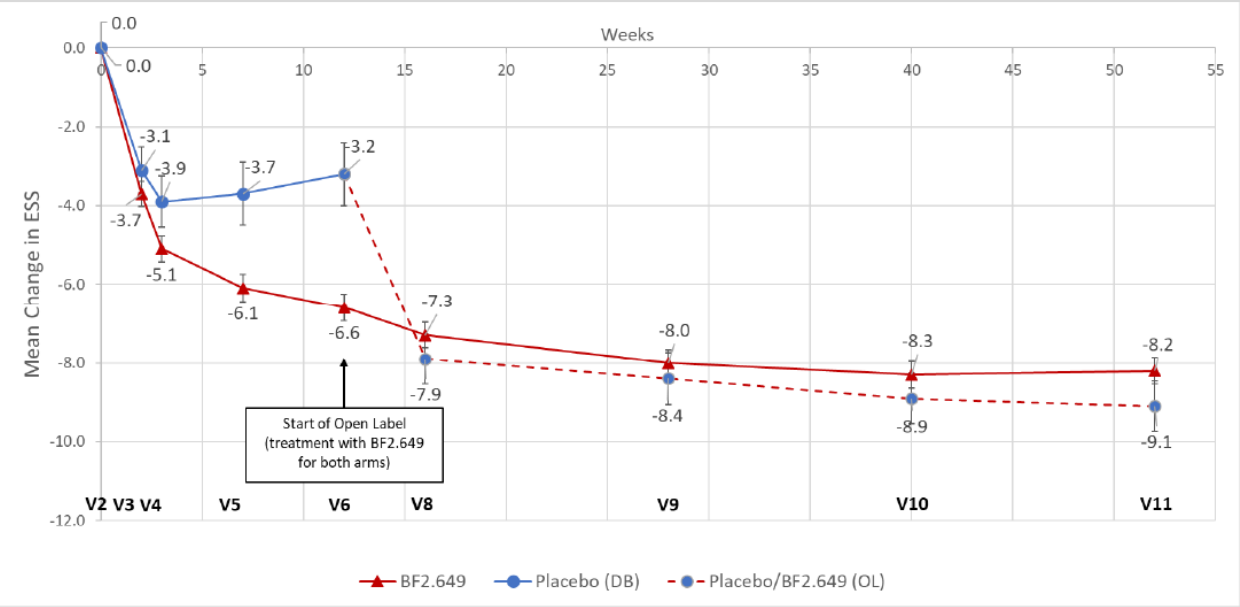
Open-label phase

ESS

At open-label baseline (V5/V6), the average (±SD) was 12.2 ± 5.6 and 9.3 ± 4.6, respectively. The mean change in ESS score between V2 and open-label baseline was -3.5 ± 5.6 in subjects treated with placebo in the double-blind phase and -6.4 ± 4.4 in the subjects treated with pitolisant during the double-blind phase of the study.

After 40 weeks of treatment with pitolisant in two groups of subjects, mean ESS score reductions from open-label baseline were -5.2 ± 5.4 in subjects treated with placebo in the double-blind phase and -1.6 ± 3.4 in the subjects treated with pitolisant during the double-blind phase of the study. For the subjects treated with pitolisant during the double-blind phase of the study, the mean decrease was -1.6 (95%CI: [-2.1;-1.1]). For the subjects treated with placebo during the double-blind phase of the study, the mean decrease was -5.2 (95%CI: [-6.6;-3.7]). See **Error! Reference source not found.**.

Figure 9. ESS Mean Change (± SE) during the Double-Blind Phase and Open Label Phase – OL-ITT Population (N=236)



ESS response

At the end of the open-label phase, R1 response (ESS ≤ 10) was observed in 77.3% (95% CI: [70.6% - 83.2%]) of the subjects treated with pitolisant during the double-blind phase, and 85.5% (95% CI: [73.3% - 93.5%]) of the subjects treated with placebo during the double-blind phase. R2 response (ESS≤10 or improvement ≥ 3) was observed in 87.8% (95% CI: [82.2% - 92.2%]) of the subjects treated with pitolisant during the double-blind phase and 96.4% (95% CI: [87.5% - 99.6%]) of the subjects treated with placebo.

Ancillary analyses

The final DBF-BOCF ESS score was analyzed using the same ANCOVA model as for the primary analysis on the ESS. This analysis also showed a statistically significant treatment effect (nominal p<0.001). Two models making use of DBF-LOCF but without controlling for BMI at V2 and for neither BMI and ESS at V2 also showed a statistically significant treatment effect (nominal p<0.001).

No subgroup analyses or exposure-response analyses were performed.

Summary of main efficacy results

The following tables summarise the efficacy results from the main study HAROSA-II supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit-risk assessment (see later sections).

Table 19. Summary of efficacy for trial HAROSA-II

Title: Efficacy and safety of BF2.649 in the treatment of Excessive Daytime Sleepiness in patients with Obstructive Sleep Apnoea syndrome (OSA) refusing the nasal Continuous Positive Airway Pressure (nCPAP) therapy			
Study identifier	P09-09 (HAROSA-II) EudraCT N°: 2009-017251-94		
Design	Randomized, double-blind, placebo-controlled, parallel-group, multicentre, fixed dose study		
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:		12 weeks 2 weeks
Hypothesis	Superiority of pitolisant vs. placebo		
Treatments groups	Pitolisant*		Pitolisant 12 weeks
	Placebo		Placebo 12 weeks
Endpoints and definitions	Primary endpoint	ESS	Change in Epworth Sleepiness Scale Score (ESS) between baseline (V2) and end of treatment (V6)

	Secondary endpoints	ESS responder	R1: reaching an absolute value of the ESS inferior to 11 R2: either reaching an absolute ESS inferior to 11 or an improvement from baseline of at least a
		Sleep diaries	Difference between the treatment groups on Mean Wakefulness duration, Mean Daily Alertness Duration, Mean Daily Number of Sleep Episodes and Mean Daily Duration of Sleep Episodes, during the table treatment period (V5
		OSleR	Difference between the treatment groups on the Oxford Sleep Resistance test (OSleR) at V6 corrected for baseline (V2)
		CGI-C	Difference between the treatment groups on Clinical Global Impression change (CGI) at V6
		PGOE	Difference between the treatment groups on Patient's Global Opinion on Efficacy (PGOE) compared to pre-study conditions
Database lock	18/04/2015		

Results and Analysis

Analysis description	**Primary Analysis**		
Analysis population and time point description	Intent to treat V6 – end of double blind		
Descriptive statistics and estimate variability	Treatment group	**Placebo**	**Pitolisant**
	Number of subject	67	201
	ESS	-3.6	-6.3
	SD	5.5	4.5
	ESS Response	R1: 44.8% R2: 53.7%	R1: 67.2% R2: 80.6%
	95% CI	R1: 32.6% ; 57.4% R2: 41.1% ; 66.0%	R1: 60.2% ; 73.6% R2: 74.4% ; 85.8%
	Sleep diaries Mean difference	SDWD: 0.21 SDAD: 0.87 SDNS: -1.30	SDWD: 0.22 SDAD: 1.01 SDNS: -1.79
	SD	SDWD: 1.04 SDAD: 1.42 SDNS: 1.86	SDWD: 1.12 SDAD: 1.44 SDNS: 1.97

	OSIeR Geometric mean	1.39	1.65
	Range	0.22 – 34.0	0.17 – 29.0
	CGIc	56.3%	84.2%
	95% CI	43.3% ; 68.6%	78.2% ; 89.1%
	PGOE		
	95% CI	47.9% - 72.9%	80.6% - 90.9%
Effect estimate per comparison	Primary endpoint **ESS**	Comparison groups	**Placebo | Pitolisant**
		LSM mean difference	-2.8
		95% CI	-4.0 ; -1.5
		P-value	*p<0.001*
	ESS response	Comparison groups	**Placebo | Pitolisant**
		Responder %	R1: 44.8% | 67.2% R2: 53.7% | 80.6%
		95% CI	R1: 32.6% ; 57.4% | 60.2% ; 73.6% R2: 41.1% ; 66.0%| 74.4% ;
		Nominal P-value *(Nonlinear logistic mixed*	*R1 p<0.001* *R2 p<0.001*
	Sleep diaries	Comparison groups	**Placebo | Pitolisant**
		LSMean difference SDWD SDAD	 -0.1 -0.0
		95%CI SDWD SDAD	 -0.4; 0.2 -0.4; 0.3
		Nominal P-value *SDWD* *SDAD* SDWS	*p=0.510* *p= 0.905* *p= 0.056* *p= 0.66*
	OSIeR	Comparison groups	**Placebo | Pitolisant**
		Geometric mean difference	1.39 | 1.65
		Range	0.22 – 34.0 | 0.17 – 29.0
		Nominal P-value	*p=0.167*

	CGI	Comparison groups	**Placebo | Pitolisant**
		% Improved	56.3% | 84.2%
		95% CI	43.3% ; 68.6%| 78.2% ; 89.1%
		Nominal P-value *(Nonlinear logistic mixed*	*p<0.001*
	PGOE	Comparison groups	**Placebo | Pitolisant**
		% Improved	60.9% | 86.3%
		95% CI	47.9% - 72.9% | 80.6% |
		Nominal P-value	*P<0.001*
Notes	* By the end of the titration period (from 5 to 20 mg/daily in pitolisant group), the stable dose was 20 mg for 75.4% of patients, 10 mg for 15.7% and 5 mg for 8.9% while in the placebo group these were 81.5%, 10.8%, and 7.7%,		

Analysis performed across trials (pooled analyses AND meta-analysis)

Three competing meta-analytical statistical models tested the effect of study and treatment in Intent to treat (Full Analysis Set).

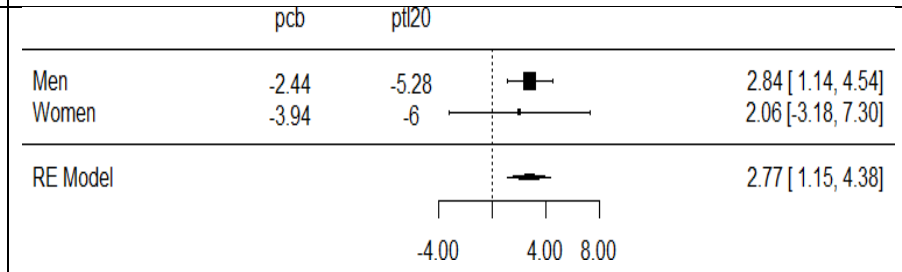
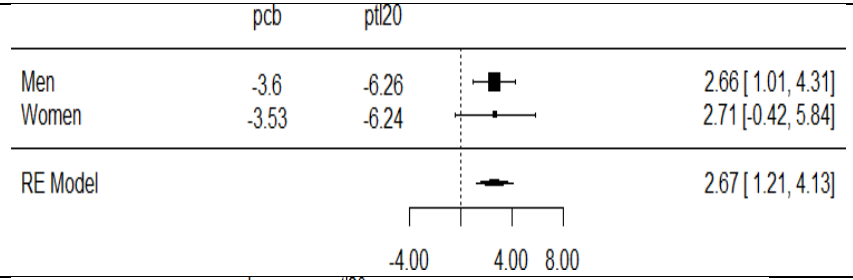
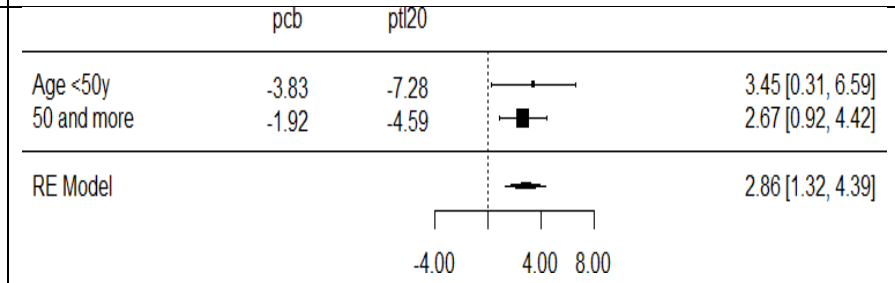
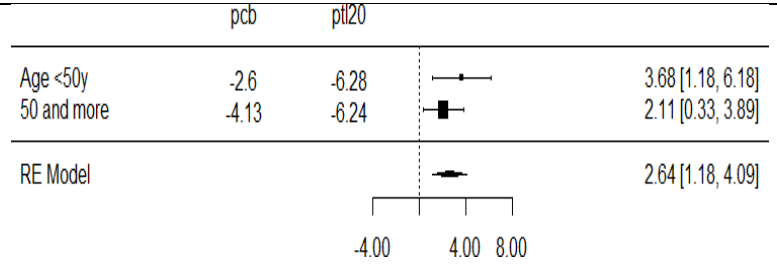
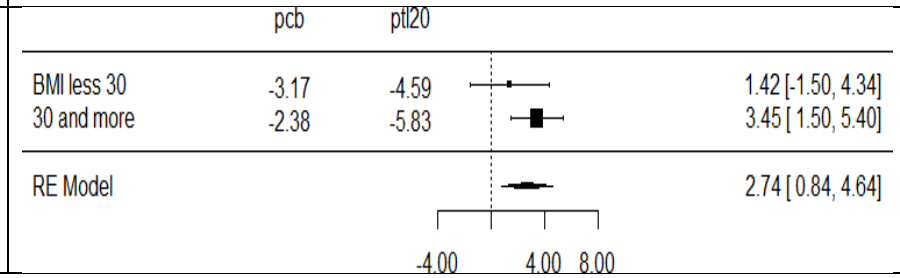
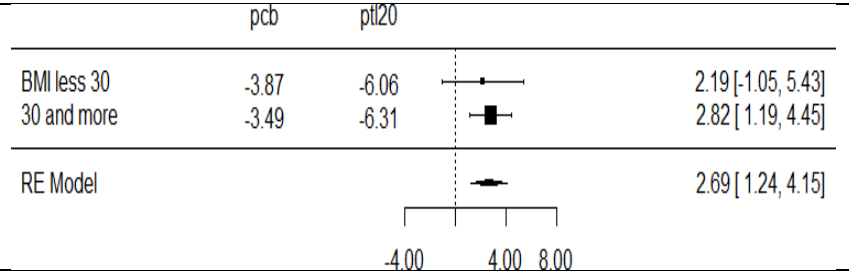
On ESS a statistically significant fixed effect of the treatment was found with a mean estimated difference between pitolisant and placebo of -2.66 [95%CI -3.58,-1.73], p<0.001), in the main RRV model, and non-significant random effects of treatment across studies (SD across studies =0.06 ([0, 0.12), p=0.541) or study effect (SD=0.03 ([0,0.8],p=0.592]). The same results were found for the 2 other models RFV and RFF. Finally, the summary mean random meta-analytical model provided the assessment of the treatment effect as pooled mean ESS difference of -2.74 ([-3.82,-1.66], p<0.001), which was found homogeneous among studies (Q-test=0.04, p=0.841, I2≅0)

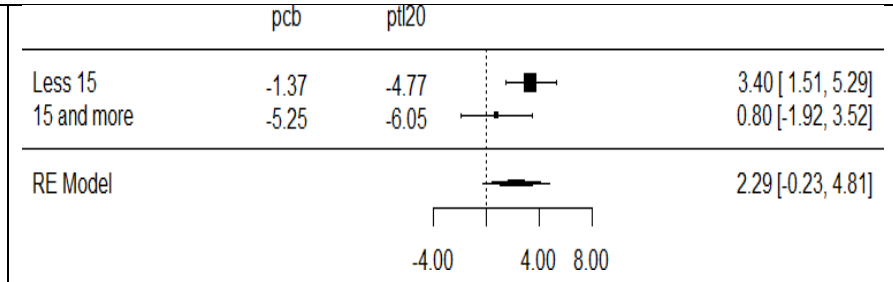
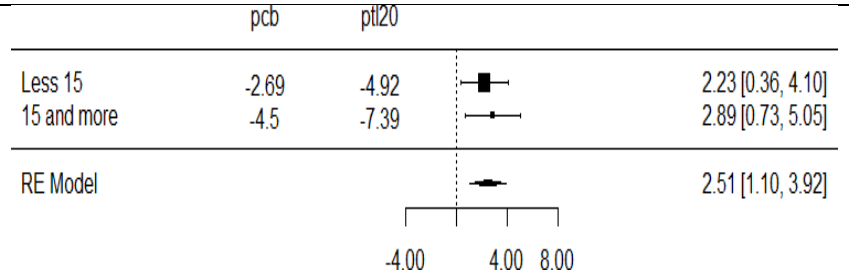
For OSLER test, a significant effect of the treatment was found with a mean estimated Final/Baseline ratio Pitolisant/Placebo of 1.16 [95%CI 1.02, 1.32], p=0.018) in the main RRV model, with non-significant random effects of treatment across studies (p=0.541) or study effect (p=0.592]. The same results were found for the 2 other models RFV and RFF. When the mean Osler ratio (Final/Baseline) was compared, in using the summary mean meta-analytical model, the pooled mean difference over the two studies (treatment effect) was 1.19 ([1.05,1.35], p=0.008), homogeneous among studies (Q-test=0.09, p=0.76, I2≅0).

Subgroup analyses

Post hoc subgroup analyses were performed for the HAROSA-I and II studies for the following subgroups of interest: sex, age, BMI and baseline ESS. See figure below for the corresponding forest plots.

Figure 10. Forest plots of subgroup analyses performed for the HAROSA-I and HAROSA-II studies

	HAROSA I	HAROSA II
Gender		
Age		
BMI		

ESS **base**		

Clinical studies in special populations

Not applicable

Supportive studies

Pilot study P04-01

Study P04-01 was a prospective, multicenter, comparative, placebo sequential controlled, single-blind study. The study was designed with 2 days of placebo treatment followed by 3 days of 40 mg pitolisant treatment, and then 2 days of placebo again in single-blind conditions after a 14-day wash-out period

The main efficacy criterion was assessed as the change in the number of diurnal sleepiness episodes (sleep agenda) and the total duration of the daily diurnal sleepiness i.e. the percentage of diurnal sleepiness (adjusted on nocturnal sleep duration). Diurnal sleepiness was also evaluated with the change of ESS score.

A total of 12 male subjects were enrolled (mean age 48.2 years; mean time since OSA onset 9.9 years; mean AHI score 56.9).

In 11 subjects, a slight and regular decrease in the number of diurnal sleepiness episodes was observed from day 1 to day 6. No statistically significant difference was observed between both treatment periods, placebo and pitolisant (mean change 0.24, p=0.38). Similarly, the change between pitolisant and placebo in the daily duration of diurnal sleepiness was not statistically significant (mean change 0:13, p=0.15).

As 3 subjects did not report any diurnal sleep, the analysis on 8 subjects showed that the mean duration of diurnal sleep significantly decreased with pitolisant in comparison with placebo (mean change=10 minutes; p=0.016).

In all 12 subjects, the mean ESS score significantly decreased from baseline (15.7) to the end of study (9.8) after the 7-day treatment period (p=0.0005).

Pilot study P05-01

Study P05-01 was a prospective, multicenter, comparative, placebo sequential controlled, single blind study. After a 14-day wash-out period, subjects received placebo for 7 days followed by 7 days of pitolisant treatment.

The main efficacy criterion was assessed as the evolution of the Osler test (simplified test to assess the ability to maintain wakefulness) with pitolisant in comparison to placebo: modifications of the sleep onset latency and the number of errors during the test. The secondary criteria were the evolution of ESS score and nocturnal polysomnography parameters. Paired t-tests were used to detect the difference between placebo and pitolisant.

A total of 21 subjects (mean age 51.33 years; mean time since OSA onset 8.5 years; mean AHI score 54.95) were included and 20 subjects completed the study.

A significant improvement was observed with pitolisant compared to placebo in the mean sleep onset latency measured at 9:00 am with the Osler test (mean difference 6.65, 95%CI [1.20, 12.10]; p<0.01). The number of microsleeps and number of errors at the Osler test decreased between baseline and end of pitolisant treatment; the improvement was not statistically significant but showed a tendency in favour of pitolisant (mean difference -1.20, 95%CI [-2.65,0.26]; p=0.057; mean difference -8.87, 95%CI [-19.88, 2.13]; p=0.082, respectively.

2.5.3. Discussion on clinical efficacy

Efficacy of pitolisant in OSA was examined in 5 double/single-blind, placebo-controlled randomized studies. The two-phase 3 studies i.e. HAROSA-I and HAROSA-II are considered pivotal for the MAA. In these studies, the dosing regime of up to 20 mg of pitolisant once daily was evaluated.

In an updated overview of the clinical studies, HAROSA-III (P15-13) was added. This recently completed (April 2020) study was a randomized, double-blind, placebo-controlled study that evaluated the efficacy and safety of 40 mg of pitolisant in the treatment of EDS in OSA patients using or refusing nCPAP treatment. Preliminary results have been submitted by the Applicant, which are considered supportive of the HAROSA-I and II studies. A dose of 40 mg pitolisant was chosen to evaluate if this had any added benefit over the 20 mg dose which was evaluated in the HAROSA-I/II studies. Information from this study could be informative to prescribers; however, the current data is too limited for a thorough assessment. The final study report will be made available for review once it is finalized, via a type II variation.

Design and conduct of clinical studies

Both main studies HAROSA-I and HAROSA-II were phase III, multicentre, randomized, double-blind, placebo-controlled study in adults with moderate to severe OSA who have (residual) EDS.

An established diagnosis of OSA by diagnostic criteria, e.g. the ICSD-3 criteria was not considered an inclusion criterion. However, it was clarified by the Applicant that the included participants were adults with an OSA diagnosed according to the ICSD-2 criteria, which were used at the time of the study.

The primary endpoint was the change in ESS between baseline (V2) and end of treatment (V6). ESS is a well-established measurement of subjective EDS and has been used extensively in sleep disorder studies, including OSA. The key secondary endpoint was the Epworth response, defined by the Applicant as reaching an absolute value of the ESS inferior to 10 (R1) and either reaching an absolute ESS inferior to 10 or an improvement from baseline of at least 3 (R2). Both endpoints are in line with previous recommendations by the CHMP through Scientific Advice.

Other important secondary endpoints were the sleep diaries which measured various variables related to EDS, the OSlER test which measured objective maintenance of wakefulness and CGI to further evaluate clinical relevance of the results obtained on the ESS.

No multiplicity correction was performed for the analysis of secondary endpoints, therefore the results of these endpoints will be seen as explorative.

In HAROSA-I compliance to nCPAP was originally planned to be measured throughout the study, but a global protocol amendment sates this was only measured at V1. However, though compliance was not documented throughout the study, nCPAP adherence was part of the routine follow-up for patients in the study. No unexpected reductions in compliance were observed.

The definitions of the analysis populations are acceptable. The primary endpoint will be analysed using a linear mixed-effects model, including baseline ESS, centre and BMI. BMI was included into the statistical model due to its high prevalence, a potentially smaller effect and lower bioavailability in patients with a higher BMI. Post hoc analysis has indicated that the inclusion of BMI into analysis did not affect the results. Secondary endpoints for both the double-blind phase and the open-label phase, were analysed with either a nonlinear logistic mixed model for categorical endpoints or a linear mixed model for continues endpoints, except for OSleR data which is analysed using a t-test on the geometric mean of the ratios between visit 6 and baseline.

Efficacy data and additional analyses

Dose-finding study P09-16

The results generally seem to indicate a dose-response starting from 10 mg pitolisant. Both the 20 mg and the 40 mg of pitolisant lead to statistically significant improvements in ESS score when compared to placebo. However, numerically 40 mg pitolisant appears to have no additional benefit over the 20 mg dose. Hence the 20 mg pitolisant dose was selected as the target dose in the main studies HAROSA-I and HAROSA-II.

HAROSA-I

The treatment groups were well balanced with respect to baseline ESS scores and disease characteristics. Baseline ESS was around 15 for both groups, which is indicative of excessive daytime sleepiness. AHI under nCPAP is around 4 for both treatment groups, indicating subjects were responsive to treatment.

Double-blind phase

By the end of the titration period, the stable dose was 20 mg for 70.3% of subjects, 10 mg for 21.1% and 5 mg for 8.6% while in the placebo group it was 81.4%, 10.2%, and 8.5%, respectively.

Pitolisant treatment resulted in a statistically significant reduction in ESS score at the end of the double-blind when compared to placebo (primary endpoint). The mean difference of change between the groups (95% CI) was -2.6 (95%CI: -3.9 to -1.4; p<0.001).

The key secondary endpoint was the ESS response. In the pitolisant group, 56.3% of subjects had an ESS score of less than 10 (R1 response), whereas this was 42.6% for the placebo group. The percentage of subjects that had either an ESS score of less than 10 or an improvement of at least 3 (R2 response) was 71.0% in the pitolisant group and 54.1% in the placebo group. For both responses, a numerical difference in favour of pitolisant was shown (nominal p=0.028 and nominal p=0.013 respectively). Based on the provided ESS responses, it cannot be eluded how many subjects actually had an improvement in ESS score of at least 3 on the ESS. Post hoc analysis provided by the Applicant has indicated that 70% of subjects in the pitolisant group and 52.5% in the placebo group had an ESS improvement of at least 3. Furthermore, the percentage of subjects who had an ESS ≤ 10 and an ESS improvement of ≥ 3 was 55.2% for the pitolisant group and 41.0% of the placebo group. In both analyses, a large placebo response can be observed, which challenges the clinical relevance of the effect.

Analysis of sleep diaries, an additional subjective measurement of daytime sleepiness next to ESS, showed some numerical improvement on the measured variables. However, there was no difference between pitolisant treatment and placebo at V6 for all variables.

Three analyses were performed on the OSleR test. Two out of three measurements showed no improvement of pitolisant on the maintenance of wakefulness compared to placebo (Geometric mean t-test, nominal p=0.076; ANCOVA $LSMean_{pitolisant\text{-}placebo}$= 0.1, nominal p=0.147). The MMRM showed a small numerical dfference ($log(OSL)_{pitolisant\text{-}placebo}$=0.2, nominal p=0.050). As the result is not replicated in any of the other analyses, it is considered that pitolisant treatment did not improve the maintenance of wakefulness when compared to placebo. Subgroup analysis seems to suggest that in patients with a more severe OSleR baseline score, the effect of pitolisant on the OSleR test was better. However, there was an overlap between the confidence intervals of the compared groups. In addition, this effect was not confirmed in the HAROSA-II study. Hence, no conclusions can be made on the role of baseline severity on alertness measured by the OSleR test.

Compared to baseline, 78% of subjects in the pitolisant group were assessed as improved in the placebo group; this was around 53%. The difference between the groups in terms of improvement was

numerically in favour of pitolisant (nominal P<0.001). More subjects in the pitolisant group were assessed as very much or much improved compared to placebo.

In the patient-reported outcome PGOE, a higher percentage of subjects in the pitolisant group considered their EDS improved compared to the placebo group (76.4% vs 56.9%, respectively, nominal p=0.005).

Open-label phase

In the open-label phase, similar reductions in ESS scores were observed for subjects who rolled over from the pitolisant and placebo groups in the double-blind phase. Maintenance of effect based on open-label results cannot be established due to the lack of a comparative arm. The evaluations of efficacy are considered explorative. The EMA guideline on insomnia (which is also used in other sleep disorder modalities) also recommends that long term efficacy be investigated in a double-blind placebo-controlled setting, such as a randomized withdrawal study or phase (EMEA/16274/2009 Rev. 1). Such a design phase has been proposed to the Applicant in the 2007 Scientific Advice, in which it was highlighted that this setup will also allow for evaluation of rebound and withdrawal. The Applicant included a one-week placebo washout phase after the double-blind phase, intending it as a withdrawal phase, only for subjects who decided to not roll over into the open-label phase. Additional analyses were provided by the Applicant to support the maintenance of effect and evaluate possible rebound effects, see below.

<u>HAROSA-II</u>

The treatment groups were well balanced with respect to baseline ESS scores and disease characteristics. Baseline ESS was around 16 for both groups, which is indicative of excessive daytime sleepiness. At the baseline polysomnography, the AHI was 47.9 for the pitolisant group and 48 for the placebo group. This indicates severe apnea for both treatment groups.

Subjects refusing nCPAP was considered an acceptable study population by CHMP (2009 SA) provided subjects would be regularly re-evaluated to check if they changed their mind on using nCPAP. It was clarified by the Applicant that subjects were re-evaluated at each study visit whether they wanted to initiate nCPAP therapy. A total of six subjects discontinued the study to do so. Subjects' reasoning for refusing nCPAP was not recorded in HAROSA-II.

The study population's baseline AHI was around 48, which is indicative of severe apnea. According to treatment guidelines, an AHI of ≥ 30 would warrant intervention, usually with nCPAP. When nCPAP is not used by a patient, these guidelines state to consider alternative treatments such as a mandibular advanced orthese or surgical interventions (e.g. NVALT [NL] or DGSM [DE]). However, stated in the exclusion criterion, other OSA interventions, either surgical or with a medical device was prohibited. Thus, subjects in the HAROSA-II study population were not receiving any kind of primary treatment for the underlying OSA.

It was agreed that concomitant use of pitolisant with primary OSA therapy should still be considered standard. However, it is acknowledged that a subgroup who cannot tolerate the primary therapy exists. Therefore, the inclusion of this subgroup into the indication is supported, as it implies that patients should have first attempted primary OSA therapy prior to starting with pitolisant. The patient decision regarding primary therapy should also be periodically rechallenged. Accordingly, a statement in the SmPC section 4.2 states that pitolisant is not a therapy for the underlying airway obstruction in patients with OSA, OSA treatment should be maintained or periodically re-challenged in patient not tolerating primary OSA therapy.

Double-blind phase

By the end of the titration period, the stable dose was 20 mg for 75.4% of subjects, 10 mg for 15.7% and 5 mg for 8.9% while in the placebo group these were 81.5%, 10.8%, and 7.7%, respectively.

Pitolisant treatment resulted in a statistically significant reduction in ESS score at the end of the double-blind phase when compared to placebo (primary endpoint). The mean difference of change between the groups (95% CI) was -2.8 (95%CI: [-4.0;-1.5; p<0.001).

An ESS R1 response was observed in 67.2% of the subjects in the pitolisant treatment group, and 44.8% in the placebo group. R2 response was observed in 80.6% of the subjects (in the pitolisant treatment group and 53.7% in the placebo group. Post hoc analysis provided by the Applicant has indicated that 79.1% of subjects in the pitolisant group and 49.3% in the placebo group had an ESS improvement of at least 3. Furthermore, the percentage of subjects who had an ESS ≤ 10 and an ESS improvement of ≥ 3 was 65.7% for the pitolisant group and 40.3% of the placebo group. In both analyses, a large placebo response can be observed, which challenges the clinical relevance of the effect.

ESS improvement was not reflected by improvement in the sleep diaries. Though there was some numerical improvement, the difference between pitolisant and placebo was not statistically significant for all variables analysed.

For the OSleR test, all three analyses performed (geometric mean, ANCOVA, MMRM) showed no difference between pitolisant and placebo on the improvement of maintenance of wakefulness.

Compared to baseline, 84.2% of subjects in the pitolisant group were assessed as improved vs around 56.3% in the placebo group. The difference between the groups in terms of improvement was numerical larger in the pitolisant group (nominal P<0.001). More subjects in the pitolisant group were assessed as very much or much improved compared to placebo.

In the patient-reported outcome PGOE, a higher percentage of subjects in the pitolisant group considered their EDS improved compared to the placebo group (86.3% vs. 60.9% respectively). The difference between the groups was numerically in favour of pitolisant (nominal p<0.001).

Open-label phase

In the open-label phase, similar reductions in ESS scores were observed for subjects who rolled over from the pitolisant and placebo groups in the double-blind. As stated before, the open-label design, e.g. lack of comparator, does not allow for conclusions of efficacy. Additional analyses were provided by the Applicant to support the maintenance of effect and evaluate possible rebound effects, see below.

<u>Overall data</u>

Overall, the effect of pitolisant seems consistent across the subgroups. There were some subgroups where a slight difference could be observed (e.g. BMI, ESS and OSLeR baseline); however, this effect was not consistent across the studies and confidence intervals were overlapping.

In both studies, around 20-30% of subjects received a dose of less than 20 mg pitolisant. Dose reduction was mostly related to headache, insomnia and gastro-intestinal discomfort, which is in line with the safety profile of pitolisant. Lower doses of pitolisant are less effective as observed in dose-finding study P09-16. Post hoc dose-response analyses were provided by the Applicant as requested. In the analysis, the 5 and 10 mg doses occasionally produce a greater improvement on an endpoint compared to the 20 mg dose. However, the difference compared to placebo is not always within the same order of magnitude as the 20 mg – placebo comparison, and in some cases the placebo group performs better. Taken together, the data suggest that the lower doses of pitolisant also produce some efficacy, and according to the SmPC the dose will be titrated based upon effect.

In the main studies, efficacy of pitolisant versus placebo was shown on the ESS with a mean reduction of -2.6 and -2.8 for HAROSA-I and HAROSA-II respectively. A reduction of more than 3 points on the ESS is considered a clinically relevant difference. Though this was not reached in the studies, clinician's assessed the subjects' as improved in the CGI and subjects also considered their condition improved in the PGOE. In addition, ESS response identified more subjects in the pitolisant groups reaching an ESS ≤ 10 compared to placebo. However, the effects on ESS were not consistently supported by other (key) secondary endpoints. Sleep diaries, which are another subjective measurement of daytime sleepiness showed no difference between the treatment groups. Most importantly, there was no effect of pitolisant on the OSleR test, which is an objective measurement of maintenance of wakefulness. This is considered surprising as in exploratory study P05-01 a statistically significant improvement on both ESS and OSleR was shown. Thus, there appears to be a benefit only in terms of ESS and CGI improvement, but not on other subjective and objective measurements of EDS. The efficacy of pitolisant in OSA is therefore considered not unequivocally shown.

To address this issue, statistical analyses were provided by the Applicant to show that there were correlations between the ESS and several secondary endpoints. In addition, it is argued that the study was insufficiently powered to detect changes on the secondary endpoints. Further information that was provided regarding the methods of the pooled analysis across the studies has shown that this analysis can be considered supportive, not confirmative.

A discussion on the totality of evidence supporting the efficacy of pitolisant to improve EDS in OSA was also provided, including a comparison against solriamfetol (Sunosi, EMEA/H/C/004893). This was considered supportive to show a relevant effect of pitolisant in the symptomatic treatment of EDS associated with OSA.

It is noted that an additional comparison against EDS improvement with CPAP therapy was also provided. However, as CPAP is a primary OSA therapy and the effects on EDS are secondary effects, pitolisant being intended as a symptomatic treatment only, this comparison was not agreed.

Pooled analysis and comparison of studies

The Applicant performed a range of analyses on the pooled data of Harosa-1 and 2. Additional information provided by the Applicant has indicated that these analyses followed a predefined SAP which was locked from the start of the study, which is reassuring. However, the basis for the marketing application are the two pivotal studies, which were powered for the primary endpoint.

Moreover, according to the meta-analysis SAP, repeating the primary endpoint analysis was not one of the objectives of the meta-analysis. Furthermore, the meta-analysis results deviate slightly because the analysis model and handling of missing data is different (linear mixed model and multiple imputation instead of ANCOVA and LOCF/BOCF), which may confuse prescribers and are therefore not considered clear. Therefore, the meta-analysis results of the primary endpoint is not reported in the SmPC. Since the pivotal studies were not powered for the secondary endpoints, they were not included in a confirmatory testing strategy, and the meta-analysis had their pooled analysis as objective, it was agreed to provide the meta-analysis results of the secondary endpoints in section 5.1 of the SmPC.

Rebound

In both HAROSA-I and II, subjects who decided to not to continue into the open-label phase of the study entered a one-week phase between V6 and V7 in which they received placebo. This one-week placebo phase was implemented to assess any potential rebound effects and additional data regarding potential rebound effects for these subjects was provided.

Between V6 and V7, subjects who received pitolisant in HAROSA-I reported an increase in mean ESS score of +1.04 and in HAROSA-II there was a decrease of -0.44. Overall, the ESS increased with +0.62.

Though the increase is small, this is suggestive that there may be some rebound effects when subjects were switched to placebo. Additionally, there a more pronounced worsening of ESS scores can be seen between V11 and V12, which was the end of the study placebo washout phase. The effect is most apparent in HAROSA-I, where a difference in mean ESS score of +1.5 and +1,8 can be seen for the DB pitolisant and DB placebo groups respectively.

Further discussion regarding a possible rebound effect was requested, including taking into account potential biases. While an increase in ESS has been observed in the time periods pitolisant treatment was withheld, it is agreed that this did not exceed baseline values. Aspects such as selection bias have not been adequately discussed. However, in view of the SmPC statement that no rebound effect was reported in the clinical studies, however treatment discontinuation should be monitored, the CHMP agreed not to pursue the issue further.

Maintenance of effect

To further substantiate maintenance of effect, the Applicant provided two statistical analyses on the pooled data from the studies: 1) minimum value of the relative maintenance and 2) expected value of the relative maintenance. The first analysis is considered not suitable to estimate maintenance, as it uses the difference between V8 and V6 to measure maintenance of pitolisant over month 4. Pitolisant dosing was not stable over this period, as V6 to V8 was the dose-escalation phase of the open-label part of the study. Furthermore, this approach compares different treatment periods (v8-v6 versus v7-v6).

The second approach is not understood, it is based on the hypothesis that the ESS value cannot decrease when treatment is interrupted. The mean ESS score at V11 (referred to as month 12 in the analysis) was compared between subjects who received pitolisant throughout the study and those who switched from placebo to pitolisant when they entered the open-label phase. Somehow, an estimate of the relative maintenance is produced, but it is not clear how this is calculated nor how it should be interpreted.

Additional statistical analyses were also presented but – due to the lack of a control arm - the maintenance of effect could not be concluded. As statement indicating that long-term efficacy data are limited and continued efficicacy of treatment should be regularly evaluated by the physician has therefore been included in SmPC section 4.2.

2.5.4. Conclusions on the clinical efficacy

Pitolisant has been shown to improve ESS scores in subjects with OSA complaining of EDS with or without nCPAP treatment. Consistency of effect has been shown across various subgroups, and additional support comes from preliminary results from the recently completed HAROSA-III study. Clinical relevance was further provided by comparing the data against Sunosi, the only other approved pharmacological treatment for excessive daytime sleepiness associated with OSA.

The CHMP agreed that the available data support the efficacy in the use of pitolisant in EDS in adult patients with OSA who have not been satisfactorily treated or who have not tolerated OSA primary therapy such as CPAP.

2.6. Clinical safety

Patient exposure

Through the data cut (31 March 2019), a total of 603 subjects with OSA were exposed to pitolisant, including 284 (47.1%) subjects treated for at least 6 months and 108 (17.9%) subjects treated for at least 1 year. 151 subjects received placebo. The majority of these patients (74.8% and 70.7% respectively) were administered a dose of 20 mg/day. The use of CPAP or not was taken into account in the safety analysis: patients treated with CPAP (OSA – CPAP), patients not treated with CPAP (OSA – NCPAP). Mean average daily dose in OSA DB pool data was 15.3 mg/day and the median was 17.8 which is lower than the recommended dose, and therefore dose-related adverse events may not have occurred or were milder in severity.

In the Total Pitolisant group of the All Indications pool (1513 subjects), most patients (79.2%, 1198/1513) were exposed to a maximal dose for more than 1 month while 315 (20.8%) patients were exposed <1 month. In the Total Pitolisant group of the All Indications pool, the majority of patients (61.1%, 924/1513 patients) received a maximal dose of 20 mg once daily pitolisant compared with 40 mg once daily (23.5%, 356/1513 patients) which was essentially administered in narcolepsy studies.
A total of 334 of 1513 patients (22.1%) received a maximal dose of pitolisant for ≥1 year, and the majority of these patients (254/334 patients; 76.0%) were administered a dose of 20 mg/day.

Age

The majority of the patient population within the OSA indication comprised adults aged 50 to 64 years or ≥65 years of age (311 of 603 patients [51.6%] and 72 of 603 patients [11.9%], respectively). In younger patients 30.3% were 35-49 years (n=183/603) and 6.1% were <34 years (n=37/603).

In other patient populations, e.g., narcolepsy disease, nearly half (140 of 303 patients, 46.2%) of the patient population within the narcolepsy indication comprised young adults (18-34 years) and received 1 to <3 months of pitolisant (171 of 303 [56.4%] patients). Elderly patients (≥65 years) made up 4.6% (14/303 patients) of the Total Pitolisant-treated narcolepsy population, and half of the elderly patients with narcolepsy received 1 to <3 months of pitolisant.

Gender

In all OSA studies, the majority of patients was male (80% versus 20 % of female in the total pitolisant OSA pool). The distribution of patients by gender was comparable between pitolisant and placebo treatment groups (82.1% and 78.6% male subjects, respectively). The distribution of age and gender were similar in patients treated with CPAP or patients refusing or non-compliant to CPAP.

In all indications pooled data, the gap between male and female proportions was smaller (1072/1513, 70.9% male versus 441/1513, 29.1% female patients).

Body mass index (BMI)

In all OSA studies, mean weight was approximately 98 kg, and the mean BMI was approximately 32.5 mg/m2. The BMI was ≥30 kg/m2 in around 70% of patients so OSA population had a majority of obese patients. In fact obesity is a comorbidity known to be highly prevalent in this disease. Only 42/603 (7%) patients had normal BMI (under 25). Based on the provided sub-group analysis comparing different BMI classes (<25, 25-30 and >30), the difference in psychiatric disorders was observed for insomnia and anxiety (16.7%, 10.4% and 6.7% and 4.8%, 2.1% and 2.2%, respectively). Furthermore, subgroup analysis for AEs, has shown a highly significant decreasing effect of the BMI (-0.039 /BMI unit, [-0.058, -0.02], p<.001) on AEs.

Concomitant medications

In all OSA studies, concomitant medication use was reported in a similar proportion of patients in the pitolisant (73.9%) and placebo (72.8%) groups of double-blind, placebo-controlled studies as well as in the SB Open Label studies (73.7%). The most commonly used therapeutic classes are ACE inhibitors, plain (125/603 patients, 20.7%), Beta blocking agents (95/603, 15.8%), Lipid modifying agents (87/603, 14.4%), Selective calcium channel blockers with mainly vascular effects (82/603, 13.6%) and Angiotensin II antagonists (78/603,12.9%). Paracetamol (86/603, 14.3%) was the only other medication taken by more than 10% of subjects in the Total Pitolisant group.

In all indications pooled data, a similar proportion of patients in the pitolisant (82.7% [863/1043 patients]) and placebo (81.5% [387/475 patients]) groups of double-blind, placebo-controlled studies. Reflective of the studies in patients with Parkinson's disease, dopaminergic agents (35.4% [535/1513]) were the most commonly taken therapeutic class.

Adverse events

In OSA studies, the majority of adverse events were classified as mild or moderate, with no evidence of a dose-related trend by maximum pitolisant dose or dose at time of AE onset. The incidence of TEAEs leading to discontinuation was low (27 of 603 patients, 4.5%). Among the 603 patients with OSA who received pitolisant, 14 patients (2.3%) experienced at least 1 SAE, and there were 3 deaths. Overview of AEs in OSA studies and comparison between CPAP and NCPAP groups are summarized in Table 18.

Table 20. Overview of Adverse Events: OSA (CPAP and NCPAP) – Safety Population

	OSA (CPAP)				OSA (NCPAP)			
	Double-Blind Placebo-Controlled		Single-Blind and Open-Label Pitolisant (N=199)	TOTAL Pitolisant (N=271)	Double-Blind Placebo-Controlled		Single-Blind and Open-Label Pitolisant (N=269)	TOTAL Pitolisant (N=332)[d]
	Placebo (N=72)	Pitolisant (N=224)			Placebo (N=79)	Pitolisant (N=244)		
	n (%) of patients				n (%) of patients			
At least 1 TEAE	24 (33.3)	107 (47.8)	107 (53.8)	152 (56.1)	23 (29.1)	77 (31.6)	81 (30.1)	130 (39.2)
At least 1 severe TEAE	2 (2.8)	18 (8.0)	17 (8.5)	30 (11.1)	3 (3.8%)	6 (2.5)	12 (4.5)	16 (4.8)
At least 1 SAE	0	2 (0.9)	10 (5.0)	11 (4.1)	0	2 (0.8)	1 (0.4)	3 (0.9)
At least 1 related TEAE	15 (20.8)	66 (29.5)	57 (28.6)	104 (38.4)	17 (21.5)	61 (25.0)	62 (23.0)	104 (31.3)
At Least 1 related severe TEAE	1 (1.4)	9 (4.0)	3 (1.5)	12 (4.4)	2 (2.5)	4 (1.6)	5 (1.9)	8 (2.4)
At least 1 related SAE	0	0	1 (0.5%)	1 (0.4%)	0	0	0	0
TEAE resulting in discontinuation	2 (2.8)	5 (2.2)	11 (5.5)	15 (5.5)	2 (2.5)	7 (2.9)	5 (1.9)	12 (3.6)

n = number of patients; SAE=serious adverse event; TEAE=treatment-emergent adverse event, CPAP: nasal Continuous Positive Airway Pressure; NCPAP: No nasal Continuous Positive Airway Pressure
Note: Patients with multiple occurrences of a preferred term are counted only once for that term in each column.
Patient with an AE resulting in discontinuation in more than 1 study is counted for each corresponding discontinuation reason from those studies in which the events occurred.
If more than 1 study had the same reasons for discontinuation for a patient, the patient was counted only once in the table for that row.

In all indications pooled data, in the double-blind, placebo-controlled studies of the All Indications pool, 50.3% of patients who received pitolisant experienced at least 1 TEAE compared with 46.7% of patients who received placebo. The proportion of patients who had at least one related-TEAE was 31.5% in pitolisant group and 24.2% in the placebo group. The time to event occurrence of AEs was not discussed in the dossier.

Table 21. Overview of Adverse Events in OSA and all indication

	OSA				All Indications			
	Double-Blind Placebo-Controlled		Single-Blind and Open-Label Pitolisant (N=468)	TOTAL Pitolisant[a] (N=603)	Double-Blind Placebo-Controlled		Single-Blind and Open-Label Pitolisant (N=1021)	TOTAL Pitolisant (N=1513)[b]
Event	Placebo (N=151)	Pitolisant (N=468)			Placebo (N=475)	Pitolisant (N=1043)		
	n (%) of patients				n (%) of patients			
At least 1 TEAE	47 (31.1)	184 (39.3)	188 (40.2)	282 (46.8)	222 (46.7)	525 (50.3)	554 (54.3)	901 (59.6)
At least 1 severe TEAE	5 (3.3)	24 (5.1)	29 (6.2)	46 (7.6)	23 (4.8)	71 (6.8)	113 (11.1)	173 (11.4)
At least 1 SAE	0	4 (0.9)	11 (2.4)	14 (2.3)	15 (3.2)	27 (2.6)	62 (6.1)	87 (5.8)
At least 1 related TEAE	32 (21.2)	127 (27.1)	119 (25.4)	208 (34.5)	115 (24.2)	329 (31.5)	332 (32.5)	604 (39.9)
At Least 1 related severe TEAE	3 (2.0)	13 (2.8)	8 (1.7)	20 (3.3)	12 (2.5)	33 (3.2)	49 (4.8)	81 (5.4)
At least 1 related SAE	0	0	1 (0.2)	1 (0.2)	7 (1.5)	5 (0.5)	3 (0.3)	8 (0.5)
TEAE resulting in discontinuation	4 (2.6)	12 (2.6)	16 (3.4)	27 (4.5)	25 (5.3)	63 (6.0)	70 (6.9)	132 (8.7)

n = number of patients; SAE=serious adverse event; TEAE=treatment-emergent adverse event
[a] Includes double-blind, placebo-controlled studies; and single-blind and open-label studies in the All OSA pool.
[b] Includes double-blind, placebo-controlled studies; and single-blind and open-label studies in the All Indications pool.
Note: Patients with multiple occurrences of a preferred term are counted only once for that term in each column.
Patient with an AE resulting in discontinuation in more than 1 study is counted for each corresponding discontinuation reason from those studies in which the events occurred.
If more than 1 study had the same reasons for discontinuation for a patient, the patient was counted only once in the table for that row.

In OSA studies, during the double-blind period, AEs occurred most frequently in the SOCs of Nervous System Disorders (16.0% vs 15.9% in the placebo group), Infections and infestations (14.5% vs 7.9% in the placebo group), Psychiatric Disorders (11.8% vs 6.0% in the placebo group), and Gastrointestinal Disorders (10.3% vs 10.3% in the placebo group). The incidence of AEs is higher in the patients with CPAP for the following SOCs: Nervous System Disorders (20.1% and 12.3%), Infections and infestations (13.8% and 4.1%), Psychiatric Disorders (13.8% and 9.8%), and Gastrointestinal Disorders (12.9% and 7.8%).

In all indications pooled data, during the double-blind period AEs occurred most frequently in the same three SOCs as in the All OSA pool, and in similar proportions of patients: Nervous System Disorders (25.0%, 379/1513), Psychiatric Disorders (20.6%, 311/1513), and Gastrointestinal Disorders (16.7%, 252/1513).

In double-blind, placebo-controlled OSA studies, a higher proportion of patients treated with pitolisant (27.1%, 127/468) had at least 1 TEAE assessed as treatment-related by the investigator during study participation compared with patients treated with placebo (21.2%, 32/151). The 3 most frequently reported treatment-related TEAEs in all DB-RCT OSA studies are headache (9.6% vs 10.6 % in DB-RCT with pitolisant and placebo respectively), insomnia (7.3% vs 4.0% in DB-RCT with pitolisant and placebo respectively) and nausea (3.2% vs 1.3 % in DB-RCT with pitolisant and placebo respectively).
The most frequently reported treatment-related TEAEs in patients who received pitolisant in double-blind, placebo-controlled studies for all indications were headache (7.2% [75/1043]), insomnia (all types) (6.4% [67/1043]), nausea (3.4% [35/1043]) and abdominal pain (2.4% [25/1043]). Related-TEAEs observed at a higher incidence (approximately two times) in the pitolisant group compared with the placebo group were insomnia (6.4% vs 3.1%), nausea (3.4 % vs 2.1%), anxiety (1.6% vs 0.2%), abdominal pain (2.4% vs 0.4%) and irritability (1.0% vs 0.4%).

Serious adverse event/deaths/other significant events

In total 14 (2.3%) SAEs other than deaths were reported in all OSA studies. The incidence of treatment-emergent SAEs in double-blind, placebo-controlled studies in the all OSA pool was 0.9% (4/468) in the pitolisant group and 0% in the placebo group. Four patients who received pitolisant in the double-blind, placebo-controlled group had an SAE (cardiopulmonary failure, irritable bowel syndrome, QT prolonged on ECG and musculoskeletal pain). None of the SAE was considered treatment-related. In single-blind and open-label OSA studies of pitolisant, a total of 11/468 patients (2.4%) experienced at least one

treatment-emergent SAE. Each SAE was only reported by one patient and only one case of hypertension was considered treatment related by the investigator.

In the All OSA studies, a total of 27/603 (4.5%) patients have prematurely discontinued pitolisant due to a TEAE. Adverse events leading to discontinuation were primarily in the Nervous System Disorders (9/603, 1.5%) including headache (5), dizziness (2), circadian rhythm sleep disorder (1), somnolence (1) and tremor (1), in Psychiatric Disorders (9/603, 1.5%) including insomnia (5), depression (2), depressed mood (1), anxiety (1), irritability (1), mood altered (1) and libido decreased (1) and in Gastrointestinal Disorders (6/603, 1.0%) including nausea (3), enterocolitis (1), dry mouth (1), and breath odour (1).

In the double-blind, placebo-controlled studies in the All Indications pool, the incidence of treatment-emergent SAEs in patients who received pitolisant (2.6%, 27/1043) was comparable with patients who received placebo (3.2%, 15/475). From 27 SAEs in pitolisant group, five patients reported seven treatment-emergent SAEs assessed as related to study treatment by the investigator (abdominal pain, constipation, malaise, general physical condition abnormal, weight decreased, confusional state, and anxiety).

In single-blind and open-label studies in the All Indications pooling, a total of 62 patients (6.1%) experienced at least 1 treatment-emergent SAE. Three treatment-emergent SAEs (spontaneous abortion, psychotic disorder, and hypertension) were assessed as related to study treatment by the investigator.

In ongoing studies, as of the data cut-off date for the safety data (31 March 2019), four SAEs were reported in the ongoing post-authorization safety study (PASS [P15-11]), and no SAE was reported in the ongoing pediatric study (P11-06). In the ongoing CUP (through a data cut-off date of 31 March 2019), two SAEs have been reported. Both cases involved pregnancies (spontaneous abortions). Neither case was considered related to treatment with pitolisant.

In the ongoing US EAP (through a data-cut-off date of 13 February 2019), five SAEs have been reported (two hospitalizations for pre-existing conditions, one alcoholic relapse, one relapse of bipolar disorder (major depressive episode) and one suicide attempts), all unrelated or unlikely related to pitolisant.

Deaths

Two death occurred in P09-09 HAROSA II trial in patients with OSA refusing CPAP. Both patients had several cardiovascular and metabolic disorders, and both deaths were considered unrelated to the treatment with pitolisant by the investigator.

Deaths occurred in other indications than OSA, were also considered unrelated to the drug. In ongoing study P15-13, death occurred in the open-label period, in an obese OSA patient not using CPAP, due to cardio-respiratory failure consecutive to severe hypoxia in early morning hours. The patient had a history of cardiovascular diseases, COPD and asthma and was under treatment of pitolisant 40 mg daily (treatment arm), bisoprolol, valsartan, hydrochlorothiazide, montelukast, fluticasone/salmeterol and tiotropium bromide (concomitant medications). Causality was assessed as "possibly related" to the investigational drug pitolisant by the investigator.

Laboratory findings

According to the applicant, mean changes from baseline in the clinical laboratory, parameters were generally small, and no clinically relevant trends or differences between treatment groups were observed for any parameter. Few patients had a maximum post-baseline worsening to Grade 3 or Grade 4 abnormalities in any laboratory parameter.

There were few patients in either pooling with elevations in ALT or AST >3xULN at any time during study participation (n=4 [0.87%] and n=10 [1.1%] in the Total Pitolisant group in the All OSA Studies and All Indications poolings, respectively).

In all indications pooled data, the percentage of patients with shifts in ALT from normal at baseline to high post-baseline was slightly higher in the open-label, single-blind studies (11.9%) the All Indications pool compared with the double-blind studies (6.4% pitolisant, 6.4% placebo). This trend in shift data was not observed for AST.

Some mild elevations in alkaline phosphatase (ALP) of >1.5xULN were observed, particularly in patients followed for a longer duration in the single-blind, and open-label studies in OSA, but none reached >2xULN. The percentage of patients with shifts in alkaline phosphatase from normal at baseline to high post-baseline were comparable between pitolisant (3.1%) and placebo (5.0%) treatment groups in the double-blind, placebo-controlled studies in the All indications pooling. The proportion of patients was also comparable in the Total Pitolisant group (8.2%).

Treatment with pitolisant was not associated with worsening of renal function based on no significant changes in creatinine levels during study participation.

Safety in special populations

Age related differences

In the All OSA pool, no trend was observed in the proportion of patients with headache (including migraine) based on age (21.6%, 18.0 %, 18.6% and 11.1% in patients 18-34 years, 35-49 years, 50-64 years and ≥65 years, respectively). In the All Indications pool, the TEAE of headache (including migraine PT) was reported more commonly in younger patients than in older patients.

In the All OSA pool, the proportion of patients with insomnia was under around 6% in younger patients treated with pitolisant (5.4% and 6.0% in patients 18-34 and 35-49 years, respectively) and was higher in older patients (12.9% and 15.3% in patients 50-64 and ≥65 years, respectively).).

In the All Indications pool, insomnia was also reported in a higher percentage of older patients around 12% for patients above 50 years compared to around 7% in younger patients.

Gender related differences

In the All OSA pool, TEAEs were reported in a higher proportion of female patients than male patients both in the double-blind, placebo-controlled studies (47.0% vs 37.2%) as well as in the Total pitolisant group (49.6% vs 46.1%) (Table 4.6.1). Individual TEAEs where incidence was higher for females than for males were headache (19.0% vs 12.0%), nausea (5.0% vs 2.7%) and insomnia (12.0% vs 6.0%).

In the All Indications pool, a similar trend in TEAE reporting was observed, with a higher proportion of female patients than male patients both in the double-blind, placebo-controlled studies (58.2% vs 47.4%) as well as in the Total Pitolisant group of the All Indications pool (65.1% vs 57.3%).

BMI related differences

In the All OSA Studies pooling, during the double-blind period, the proportion of patients with at least 1 TEAE in each BMI categories of <25 kg/m2, 25 to <30 kg/m2, ≥30 kg/m2, were 21/33 (63.6%), 48/100 (48%), 115/335 (34.3%), in pitolisant group. In placebo group these proportions were , 2/6 (33.3%), 17/41 (41.4%), 28/104 (26.9%), respectively.

In all indications pooled data, during double blind period, the proportion of patients with at least 1 TEAE in each BMI categories of <25 kg/m2, 25 to <30 kg/m2, ≥30 kg/m2, were 143/228 (62.7%), 163/314

(51.9%) and 204/470 (43.4%), in pitolisant group. In placebo group these proportions were , 47/91 (51.6%), 87/173 (50.2%), 79/190 (41.6%), respectively.

The incidence or distribution of treatment-emergent SAEs between BMI subgroups in the All OSA Studies pooling or the All Indications pooling were comparable.

Differences related to renal function

In patients for whom the renal function was evaluated at baseline, the majority of patients (approximately 85% or more) in double-blind placebo-controlled studies and in the Total Pitolisant group were classified as having a normal renal function (eGFR ≥90 mL/min/1.73m2) or mild renal insufficiency (eGFR 60 to <90 mL/min/1.73m2) in both poolings. However, in OSA pooled data, the proportion of patients with the normal renal function was only 45%. There were no patients with severe renal insufficiency in either pooling as it was an exclusion criteria for all studies.

Proportions of TEAEs by renal function categories were comparable between pitolisant and placebo groups during the double-blind period in both All OSA and All indications pooling.

Differences related to hepatic function

In patients for whom the hepatic function was evaluated at baseline, the majority of patients (>65%) in double-blind placebo-controlled studies and in the Total Pitolisant group were classified as having a normal hepatic function in both poolings. Few patients (<12%) were classified as having a mild hepatic impairment at baseline. There were no patients with moderate or severe hepatic impairment in either pooling as it was an exclusion criterion for all studies.

The incidence of TEAEs during the double-blind period of OSA indication were as follow between placebo and pitolisant groups, respectively: in patients normal hepatic function: 20/100 (20%) versus 112/304 (36.8%) and in patients with mild to moderate hepatic impairment: 7/19 (36.8%) versus 15/51 (29.4%).

The incidence of TEAEs during the double-blind period of All indication pooling were as follow between placebo and pitolisant groups, respectively: in patients normal hepatic function: 60/198 (30.3%) versus 171/427 (40%) and in patients with mild to moderate hepatic impairment: 13/32 (40.6%) versus 23/65 (35.4%).

Extrinsic Factors

The use of concomitant CPAP

In patients treated with CPAP, the incidence of TEAE was higher than in patients without CPAP (56.1% and 39.2%, respectively). AEs occurred in the same SOCs, i.e. Nervous System Disorders (20.1% and 12.3%), Infections and infestations (13.8% and 4.1%), Psychiatric Disorders (13.8% and 9.8%), and Gastrointestinal Disorders (12.9% and 7.8%). The TEAE profile of pitolisant-treated patients with CPAP or without CPAP was consistent with all pitolisant-treated patients in double-blind, placebo-controlled OSA studies. The most frequently reported TEAEs in these subgroups were headache (16.1% and 11.5%), insomnia (11.2% and 6.6 %), nausea (3.1% and 3.3%) and abdominal pain (3.1 and 2.0%).

Safety related to drug-drug interactions and other interactions

Concomitant administration of pitolisant with modafinil, CYP3A4 inhibitors, and CYP2D6 inhibitors have been studied clinically. Overall, TEAEs were comparable between pitolisant alone or coadministrations with Paroxetine, Itraconazole, Rifampicin, Probenecid, Modafinil or sodium oxybate. No new safety concerns are raised by these interaction studies.

More TEAEs were reported during administration of olanzapine and pitolisant:

Study P03-08 was an open-label, fixed sequence, five-period study to evaluate the PK and PD of single oral doses of pitolisant and olanzapine, administered alone and in combination. Co-administration of olanzapine 5 mg with pitolisant HCl 60 mg decreased olanzapine exposures, with Cmax and AUC, approximately 30% and 24% lower, respectively, of those observed when 5 mg olanzapine was administered alone. Three TEAEs out of total 36 mild to moderate TEAEs were reported during pitolisant alone treatment period (dizziness (n=1) and headache (n=2)), 1/36 during the placebo treatment period and 32/36 during co-administration of olanzapine and pitolisant periods, the most frequent being somnolence (n=19) and middle insomnia (n=5).

Discontinuation due to AES

In the All OSA studies, 27 of 603 (4.5%) patients have prematurely discontinued pitolisant due to a TEAE. In the double-blind, placebo-controlled studies in OSA, the incidence of discontinuation was 2.6% [12/468 patients] and 2.6% [4/151 patients] in pitolisant and placebo groups, respectively.
Adverse events leading to discontinuation were primarily in the Nervous System Disorders (9/603, 1.5%) including headache (5), dizziness (2), circadian rhythm sleep disorder (1), somnolence (1) and tremor (1), in Psychiatric Disorders (9/603, 1.5%) including insomnia (5), depression (2), depressed mood (1), anxiety (1), irritability (1), mood altered (1) and libido decreased (1) and in Gastrointestinal Disorders (6/603, 1.0%) including nausea (3), enterocolitis (1), dry mouth (1), and breath odour (1).

In All Indications pooling, TEAEs resulting in discontinuation were observed at 8.7%, 132/1513 of patients. The incidence of TEAEs that led to discontinuation of study treatment in double-blind, placebo-controlled studies in the All Indications pool were 6.0% (63/1043) in pitolisant and 5.3% (25/475) in placebo treatment groups. The most frequently reported TEAEs resulting in discontinuation of study treatment in the pitolisant group and observed at a greater incidence than placebo were insomnia, headache, nausea and anxiety.
The most frequent (≥1%) TEAE leading to discontinuation of study treatment in the open-label Pitolisant group was insomnia (1.1%, 16/1513 patients).

Supportive safety data

Abuse potential

The results from Phase I Human Abuse Potential (HAP) study, along with analysis of data from OSA indication pool and All indications pool data (see clinical safety assessment), do not show any signal suggestive of risk of misuse or abuse with pitolisant.

Withdrawal and Rebound

Amphetamine-like withdrawal symptoms were assessed in eight clinical trials within narcolepsy after 7- or 8-week treatment duration, Parkinson's disease (EDS-PD) after 12-week treatment duration and OSA after 12-week treatment duration followed by 40-week open-label phase.

In OSA studies, withdrawal symptoms were assessed in HAROSA I and HAROSA II in all patients after the double-blind period for the patients who did not continue in the extension, and at the end of the 9-month open label period for those for continued.

Actively reported AEs with an onset within the first 7 after the last dose of study drug or spontaneously reported AEs within 30 days after the last dose of study drug were comparable in double-blind period (1.3% placebo versus 0.4% pitolisant) and around 4% in the All OSA Studies pooling during open-label period.

In All indications pooled data, the most frequently reported symptoms after discontinuation of treatment were fatigue and insomnia or hypersomnia. Only eight patients reported amphetamine-like withdrawal syndrome based on the association of dysphoria with two other symptoms: four patients treated with modafinil (4.2%), two patients treated with placebo (1.5%), and two patients treated with pitolisant (1.2%). After 7 days, the incidence of TEAEs in the Total Pitolisant group was 3.0% (46/1513 patients). Headache (3/1513, 0.2%) was the most frequently reported TEAE. After 30 days, the incidence of TEAEs in the Total Pitolisant group of the All Indications pool was 3.8% (58/1513 patients).

Long-term safety

The most frequently reported TEAEs in the All OSA Studies pooling with an onset between 6 months to <1 year were in the SOCs of Infections and infestations (5.9%), Musculoskeletal and connective tissue disorders (4.6%) and Nervous system disorders (2.8%).

TEAEs with an onset between 6 months and <1 year that were reported in more than 1 patient in the Total Pitolisant group (N=603) were influenza (7 patients), back pain (6 patients), anxiety (6 patients), viral upper respiratory tract infection (5 patients), headache (4 patients), arthralgia (3 patients), bronchitis (3 patients), pyrexia (3 patients), hypertension (3 patients), dizziness (2 patients), gastritis (2 patients) and cough (2 patients).

The most frequently reported TEAEs in the All OSA Studies pooling with an onset ≥1 year after initiation of treatment were in the SOCs of Nervous system disorders (2.8%)

TEAEs with an onset ≥1 year after starting pitolisant that were reported in ≥1% of patients in the Total Pitolisant group (N=603) were headache (3 patients).

2.6.1. Discussion on clinical safety

From the safety database all the adverse reactions reported in clinical trials <and post-marketing> have been included in the Summary of Product Characteristics.

The safety of Pitolisant in EDS treatment of OSA patients was evaluated in two main studies: HAROSA-I and HAROSA-II. The Applicant has pooled the safety data from the OSA studies, and another time OSA and non-OSA studies together (All indications pooled data). Pooling data from different clinical trials for overall safety is not optimal as the safety profile of different diseases may confound with the safety results. All indications pool also includes OSA patients, which may dilute the differences between all indications pooled group and OSA group.

A total of 603 subjects received at least 1 dose of pitolisant in the completed OSA studies.

Adverse events

The most common treatment related TEAEs during double blind placebo-controlled all OSA studies were headache (10.6% placebo versus 9.6% pitolisant), insomnia (4.0% placebo versus 7.3% pitolisant), nausea (1.3% placebo versus 3.2% pitolisant), abdominal pain (0.7% placebo versus 2.3% pitolisant), vertigo (1.3% placebo versus 1.5% pitolisant), anxiety (0% placebo versus 1.3% pitolisant) and diarrhoea (0.7% placebo versus 1.3% pitolisant).

In the open-label phases, where all subjects received study medication, adverse events were reported with a relative similar incidence compared to the double-blind period. The most common treatment-related TEAEs were headache (12.4%, 75/603), insomnia (8.9%, 54/603), nausea (3.3%, 20/603), abdominal pain (2.8%, 17/603) and anxiety (2.2%, 13/603), in all OSA indication pooled data, during the open-label period. 27/603 (4.5%) patients had to discontinue their medication due to adverse events in pitolisant group.

Most of the adverse events were of mild or modest intensity. During the double-blind period in pitolisant group 4/468 (0.9%) of patients experienced at least 1 SAE (cardiopulmonary failure, irritable bowel syndrome, QT prolonged on ECG and musculoskeletal pain), no cases of SAEs were reported in the placebo group (0/151). Neither SAE was considered treatment-related. In the open-label phase, reporting of serious adverse events was higher compared to the double-blind phase. Among the 603 patients with OSA who received pitolisant during the open-label period, 14 patients (2.3%) experienced at least 1 SAE. Only one case of hypertension was considered treatment-related by the investigator.

Adverse events of special interest

Depression, hepatic toxicity and renal toxicity were defined as AEs of special interest. In All indications pooled data, the incidence rate of these AEs was in general low and comparable with placebo group during double-blind periods.

Laboratory and physiological findings

In general laboratory findings were comparable between placebo a pitolisant based on the delivered analysis in all indications pooled data. However, uncertainties remain on overall conclusions as a limited number of subjects contributed data for laboratory findings. In most cases, only around half of the subjects, who contributed data to laboratory findings, were included in statistical analysis. Furthermore, the discussion summary of clinical safety regarding laboratory findings is too general, not classified and mostly the applicant's interpretation of the data.

Overall physiological findings (including ECG findings) were comparable between placebo and pitolisant groups during the double-blind period. Furthermore, during the open-label period, the incidences were also comparable with a double-blind period for both OSA, and All indication pooled data. Phase 1 QT clinical studies have shown the effects of pitolisant on QTcF interval at supra-therapeutic doses. In these studies, following pitolisant doses of 160 mg, 200 mg and 240 mg, the ΔQTcF was >5 ms at the three doses, which are considerably higher than the intended dose for the proposed indication. Two SAEs of sinus tachycardia and chest discomfort in one patient with narcolepsy were reported from PASS and considered as possibly related to Wakix®, which was uptitrated to 31.5mg per day in this patient. No new safety concerns are raised in this regard.

Adverse events in special population

Overall around 80% of safety data in OSA indication was contributed from male subjects and subjects with BMI above 30 kg/m2 (70%). In the All OSA pool, TEAEs were reported in a higher proportion of female patients than male patients in the double-blind, placebo-controlled studies (47.0% vs 37.2%). Similarly, data on patients with normal BMI are scarce, and available data show a higher rate of TEAEs in this group.

In the All OSA pool, the proportion of patients with insomnia was higher in older patients treated with pitolisant (5-6% in patients under 50 years compared to 12.9% and 15.3% in patients 50-64 and ≥65 years, respectively).

Incidence of TEAEs was higher in OSA-CPAP group compared to OSA-NCPAP group (56.1% versus 30.1%).

Overall data about effects on pregnancy (considering embryotoxicity in animal studies, one possible case of embryotoxicity in human clinical trials related to pitolisant and lack of post-marketing data) are inconclusive for clinical decision making.

2.6.2. Conclusions on the clinical safety

The overall safety profile of subjects in OSA studies, who received pitolisant during the double-blind placebo-controlled period, was comparable to the safety profile of those patients in All indications pooled data and safety profile of Wakix. The most common treatment-related TEAEs during double-blind placebo-controlled all OSA studies were headache, insomnia, nausea, abdominal pain, vertigo, anxiety and diarrhoea.

The remaining uncertainties are mostly due to lack of data (in female, normal weight and use during pregnancy) and are correctly reflected in the SmPC.

The CHMP agreed that the available safety data are sufficient to allow a benefit-risk assessment for the application.

To further characterise cardiovascular safety profile and long -term safety of pitolisant, the Applicant has committed to conduct a PASS study.

2.7. Risk Management Plan

Safety concerns

Summary of safety concerns

The applicant identified the following safety concerns in the RMP:

Table 22. Table SVIII.1: Summary of safety concerns

Summary of safety concerns	
Important identified risks	None
Important potential risks	Long term risks of body weight increase Cardiovascular events including QT-interval prolongation Adverse effects on reproductive function Adverse effects on embryofoetal development
Missing information	Long-term safety

Having considered the data in the safety specification, the CHMP agrees that the safety concerns listed by the applicant are appropriate.

Pharmacovigilance plan

Summary of additional PhV activities

Table 23. Table Part III.3: On-going and planned additional pharmacovigilance activities

Study **Status**	**Summary of objectives**	**Safety concerns addressed**	**Milestones**	**Due dates**
Category 3 - Required additional pharmacovigilance activities				
A multi-center, observational post-authorization safety study to compare the cardiovascular and long-term safety of Ozawade® in patients with obstructive sleep apnoea treated or not by CPAP and exposed or not to Ozawade® according to the therapeutic indication in the SmPC, when used in routine medical practice. (P21-02 - Cardiovascular risk and Long-term safety PASS) Planned	Primary - Cardiovascular risk (Cardiovascular events including QT-interval prolongation) in OSA patients treated with Ozawade® compared with Ozawade®-unexposed patients with OSA - Long-term safety of pitolisant in patients with obstructive sleep apnoea treated with Ozawade according to the agreed therapeutic indication in the SmPC	- Long-term safety - Cardiovascular events including QT-interval prolongation	Start of data collection End of data collection Study progress reports Interim reports Final report	Q4 2022 Q4 2030 Yearly Yearly 31/12/2031

Overall conclusions on the PhV Plan

The PRAC, having considered the data submitted, is of the opinion that the proposed post-authorisation PhV development plan is sufficient to identify and characterise the risks of the product.

Risk minimisation measures

Table Part V.3: Summary table of pharmacovigilance activities and risk minimisation activities by safety concern:

Identified Risks

None

table 24. Potential risks

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Long term risks of body weight increase	Routine risk minimization measures SmPC § 4.4 SmPC § 4.8 PL section 2 PL section 4 Medicinal product subject to special medical prescription Treatment should be initiated by a healthcare professional experienced in the treatment of OSA and cardiovascular risk No additional risk minimisation measure	None
Cardiovascular events including QT-interval prolongation	Routine risk minimization measures SmPC § 4.4 SmPC § 4.5 SmPC § 4.8 SmPC § 5.3 PL Section 2 PL Section 4 Medicinal product subject to special medical prescription Treatment should be initiated by a healthcare professional experienced in the treatment of OSA and cardiovascular risk No additional risk minimisation measures	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: Cardiovascular risk and Long-term safety PASS (P21-02) Final report of study results Q4 2031

Adverse effects on reproductive function	Routine risk minimization measures SmPC § 4.3 SmPC § 4.6 SmPC § 4.8 SmPC § 5.3 PL Section 4 Medicinal product subject to special medical prescription Treatment should be initiated by a healthcare professional experienced in the treatment of OSA and cardiovascular risk No additional risk minimisation measure	None
Adverse effects on embryofoetal development	Routine risk minimization measures SmPC § 4.3 SmPC § 4.4 SmPC § 4.5 SmPC § 4.6 SmPC § 5.3 PL Section 2 Medicinal product subject to special medical prescription Treatment should be initiated by a healthcare professional experienced in the treatment of OSA and cardiovascular risk No additional risk minimisation measure	None

table 25. Missing information

Safety concern	**Risk minimisation measures**	**Pharmacovilance activities**
Long-term safety	Routine risk minimization measures SmPC § 4.8 and 4.4 PL sections 2 and 4	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None

Safety concern	Risk minimisation measures	Pharmacovilance activities
	Medicinal product subject to special medical prescription Treatment should be initiated by a healthcare professional experienced in the treatment of OSA and cardiovascular risk No additional risk minimisation measures	Additional pharmacovigilance activities: Cardiovascular risk and Long-term safety PASS (P21-02) Final report of study results Q4 2031

Overall conclusions on risk minimisation measures

The PRAC having considered the data submitted was of the opinion that:

The proposed risk minimisation measures are sufficient to minimise the risks of the product in the proposed indication(s).

Conclusion

The CHMP and PRAC considered that the risk management plan version 1.0 is acceptable.

2.8. Pharmacovigilance

Pharmacovigilance system

The CHMP considered that the pharmacovigilance system summary submitted by the applicant fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

Periodic Safety Update Reports submission requirements

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

2.9. New Active Substance

The CHMP, based on the available data, considers that pitolisant is not a new active substance, as it is a constituent of a medicinal product previously authorised within the European Union. Pitolisant is contained in the marketing authorisation for Wakix which was authorised in the European Union in 2016.

2.10. Product information

2.10.1. User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the applicant show that the package leaflet meets the criteria for readability as set out in the *Guideline on*

the readability of the label and package leaflet of medicinal products for human use.

2.10.2. Labelling exemptions

A request to omit certain particulars from the labelling as per Art.63.1 of Directive 2001/83/EC has been submitted by the applicant and has been found acceptable by the QRD Group for the following reasons:

Minimum particulars can be used based on the limited space of the label.

The particulars to be omitted as per the QRD Group decision described above will however be included in the Annexes published with the EPAR on EMA website and translated in all languages but will appear in grey-shaded to show that they will not be included on the printed materials.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

Obstructive Sleep Apnea (OSA) is a disorder characterised by apnoea and hypoapnoea which are caused by a partial or complete collapse of the upper airways. Excessive daytime sleepiness (EDS) is a major complaint in patients with OSA. Daytime sleepiness reduces productivity and, during the course of the disease, also impairs cognitive ability, social compatibility, and quality of life. OSA patients can still experience EDS despite compliant and adequate use of nasal Continuous Positive Airway Pressure therapy (nCPAP).

Ozawade is intended as a symptomatic treatment to reduce EDS.

3.1.2. Available therapies and unmet medical need

The only approved pharmacological therapy for treating EDS in patients with OSA is Sunosi (solriamfetol, EMEA/H/C/004893). Sunosi is approved as an add-on treatment for EDS on top of primary OSA therapy if the patient does not have a satisfactory response with primary OSA therapy alone.

nCPAP is the treatment of choice for most patients with OSA, which aims to stabilise the upper airway. When appropriately used, nCPAP reduces the apnoea and hypopnoea rate and also improves EDS. However, some patients still complain of residual EDS despite compliant use of nCPAP. There are also patients who refuse or cannot tolerate nCPAP, and therefore suffer from EDS.

In view of compliance issues for nCPAP, or residual excessive sleepiness despite nCPAP treatment, alternative modalities such as symptomatic pharmacologic treatment may be of great interest to treat persistent residual EDS.

As of January 2020, Sunosi has been approved for the treatment of EDS in OSA whose EDS has not been satisfactorily treated by primary OSA therapy. Solriamfetol is a dopamine and norepinephrine reuptake inhibitor with several risk minimisation measures in place for cardiovascular safety.

Pitolisant provides a novel mechanism of action as a selective histamine H3 receptor antagonist/inverse agonist. As such, pitolisant could be an alternative to solriamfetol.

3.1.3. Main clinical studies

Both main studies, HAROSA-I and HAROSA-II, had a randomised, double-blind, placebo-controlled parallel-group design. HAROSA-I included patients with OSA that were treated with nCPAP but still complained of EDS (n=244). HAROSA-II was performed in subjects refusing nCPAP treatment (n=268). In both studies, the use of other primary OSA therapies was prohibited.

Both studies consisted of two parts: a 12-week double-blind phase and a 40-week open-label phase. After randomization, subjects were titrated over the course of 3 weeks up to 20 mg pitolisant and received a stable dose over the remain 9 weeks of the double-blind period. When subjects rolled over into the open-label study, they were first treated with placebo for 1 week (V6-V7 "withdrawal") and then entered another 21 day dose-escalation phase before receiving a stable dose for the remained of the open-label phase.

The primary endpoint was the change from baseline in Epworth Sleepiness Scale Score (ESS) between pitolisant and placebo. The ESS is a subjective measurement of EDS. Key secondary endpoints were the Epworth response, defined by the Applicant as reaching an absolute value of the ESS inferior to 10 (R1) and either reaching an absolute ESS inferior to 10 or an improvement from baseline of at least 3 points (R2). Wakefulness and sleepiness episodes were evaluated through sleep diaries. Further maintenance of wakefulness was assessed via the Oxford Sleep Resistance test (OSleR), which is an objective measurement, and the Clinical Global Impression (CGI) provided an overall evaluation of whether subjects' EDS was improved compared to baseline.

3.2. Favourable effects

In HAROSA-I, the mean change in ESS score (SD) from baseline to V6 was -2.75 (5.90) for the placebo group and -5.52 (4.41) for the pitolisant group. The LS mean difference (95% CI) between placebo and pitolisant was -2.6 (-3.9 to -1.4) and was statistically significant (2-sided p< 0.001).

R1 response (ESS≤10) was observed in 42.6% of subjects (95% CI: [30.0% - 55.9%]) in the placebo group and in 56.3% of the subjects (95% CI: [48.8% - 63.6%]) in the pitolisant group. R2 response (ESS≤10 or improvement ≥3) was observed in 54.1% of subjects (95% CI: [40.8% - 66.9%]) in the placebo group and in 71.0% of the patients (95% CI: [63.9% - 77.5%]) in the pitolisant group. A numerical difference was shown in favour of pitolisant on both responses.

In the OSleR test the geometric mean ratio of sleep latency (OSL V6/V2) was 1.22 in the placebo group and 1.44 in the pitolisant group. There was no numerical difference in geometric mean of the ratios different between the two treatment groups.

53.4% of subjects in the placebo group and 78.0% of the pitolisant group were assessed as being improved (incl. very much, much and minimally improved) at V6 on the CGI. There was a numerical difference in favour of pitolisant between the treatment groups.

56.9% of subjects in the placebo group and 76.4% of the pitolisant group evaluated their condition improved at V6 on the PGOE.

In HAROSA-II, the mean change in ESS score (SD) from baseline to V6 was -3.6 (5.5) for the placebo group and -6.3 (4.5) for the pitolisant group. The LS mean difference (95% CI) between placebo and pitolisant was -2.8 (-4.0 to -1.5) and was statistically significant (2-sided p< 0.001).

R1 response (ESS≤10) was observed in 44.8% of subjects (95% CI: [32.6% ; 57.4%]) in the placebo group and in 67.2% of the subjects (95% CI: [60.2% ; 73.6%]in the pitolisant group. R2 response (ESS≤10 or improvement ≥3) was observed in 53.7% of subjects (95% CI: [41.1% ; 66.0%]) in the

placebo group and in 80.6% of the patients (95% CI: [74.4% ; 85.8%]) in the pitolisant group. A numerical difference was shown in favour of pitolisant on both responses.

In the OSleR test the geometric mean ratio of sleep latency (OSL V6/V2) was 1.39 in the placebo group and 1.65 in the pitolisant group. There was no numerical difference between the geometric mean of the ratios of the two treatment groups.

In the placebo group, 56.3% of subjects in the placebo group and 84.2 % of the pitolisant group were assessed as improved at V6 on the CGI.

60.9% of subjects in the placebo group and 86.3% of the pitolisant group evaluated their condition as improved at V6 on the PGOE.

To substantiate the clinical relevance of the effect, the Applicant compared the results from the Ozawade studies to those obtained in the solriamfetol studies (Sunosi ®). The results on the ESS with pitolisant fall within the range of ESS scores seen with the dose range of solriamfetol (see Sunosi EPAR EMEA/H/C/004893). A comparison between objective measurements of attention/arousal was not made; it is assumed this is due to the difference in tests (OSleR vs Maintenance of Wakefulness Test) between the studies.

Subgroup analyses were provided by the Applicant, which overall show a consistent effect of pitolisant across the subgroups.

3.3. Uncertainties and limitations about favourable effects

Secondary endpoints that measure EDS in a different modality, such as sleep diaries and OSleR show no statistically significant differences between the pitolisant and placebo group and thus did not support the primary endpoint results.

Importantly, regarding the testing strategy of the secondary endpoints, there was no hierarchy across analyses and p-values, and confidence intervals were not adjusted for multiple testing; therefore, the results should be interpreted as explorative. This further hinders the assessment of the clinical relevance of the observed effects on the primary endpoint.

In the open-label phases of both studies, further reductions in ESS scores were observed in both the former pitolisant and placebo groups. The insomnia guideline recommends that long term efficacy in sleep disorders should be investigated in a double-blind, placebo-controlled setting. Interpretation of maintenance of effect in HAROSA-I/II is hampered due to the open-label design of the phase, i.e. lack of a comparative arm. Additional statistical analyses to support maintenance of effect were either unsuitable or could not be interpreted. However, a statement has been included into the SmPC which states that long-term efficacy data is limited and the physician should regularly evaluate the efficacy of treatment. This is considered sufficient to cover this uncertainty.

Based on the additional analyses, it appears that there is some rebound when pitolisant treatment is discontinued. This is observed in both the placebo "withdrawal" phase between the double-blind and open-label phase as well as the end of study placebo washout phase. This increase does not exceed baseline ESS scores; hence it is not considered a rebound effect. Not all uncertainties regarding this aspect have been adequately discussed. A statement was included in the SmPC to state that although no rebound was reported in the clinical studies, treatment discontinuation should be monitored.

3.4. Unfavourable effects

The most common treatment related TEAEs during double blind placebo-controlled all OSA studies were headache (10.6% placebo versus 9.6% pitolisant), insomnia (4.0% placebo versus 7.3% pitolisant), nausea (1.3% placebo versus 3.2% pitolisant), abdominal pain (0.7% placebo versus 2.3% pitolisant), vertigo (1.3% placebo versus 1.5% pitolisant), anxiety (0% placebo versus 1.3% pitolisant) and diarrhoea (0.7% placebo versus 1.3% pitolisant). The most common treatment related TEAEs were headache (12.4%, 75/603), insomnia (8.9%, 54/603), nausea (3.3%, 20/603), abdominal pain (2.8%, 17/603) and anxiety (2.2%, 13/603), in all OSA indication pooled data, during open label period.

Most of the adverse events were of mild or modest intensity. Among the 603 patients with OSA who received pitolisant, 14 patients (2.3%) experienced at least 1 SAE and there were 2 deaths in patients with OSA refusing CPAP, unrelated to pitolisant treatment and 1 death was reported in HAROSA III as "probably unrelated" to pitolisant treatment.

27/603 (4.5%) patients had to discontinue their medication due to adverse events in pitolisant group.

In the All OSA pool, the proportion of patients with insomnia was higher in older patients treated with pitolisant (5-6% in patients under 50 years compared to 12.9% and 15.3% in patients 50-64 and ≥65 years, respectively).

In the All OSA pool, TEAEs were reported in a higher proportion of female patients than male patients in the double-blind, placebo-controlled studies (47.0% vs 37.2%).

Patients with normal BMI had a higher rate of TEAEs, mostly headache and insomnia.

More TEAEs were reported during administration of olanzapine and pitolisant compared to pitolisant alone period (32/36 compared to 3/36).

Phase 1 QT clinical studies have shown the effects of pitolisant on QTcF interval at supra-therapeutic doses. In these studies, following pitolisant doses of 160 mg, 200 mg and 240 mg, the ΔQTcF was >5 ms at the three doses, which are considerably higher than the intended dose for the proposed indication. Two SAEs of sinus tachycardia and chest discomfort in one patient with narcolepsy were reported from PASS and considered as possibly related to Wakix®, which was uptitrated to 31.5mg per day in this patient.

3.5. Uncertainties and limitations about unfavourable effects

Incidence of TEAEs was higher in OSA-CPAP group compared to OSA-NCPAP group (56.1% versus 30.1%). This is reflected in the SmPC.

The mean average daily dose in OSA DB pool data was 15.3 mg/day, and the median was 17.8 which is lower than the recommended dose, and therefore dose-related adverse events may not have occurred or were milder in severity. However, the safety profile of different dosing regimens is comparable with each other.

Data on female subjects are limited and show a less favourable safety profile compared to the male subjects. Overall data about effects on pregnancy (considering embryotoxicity in animal studies, one possible case of embryotoxicity in human clinical trials related to pitolisant and lack of post-marketing data) are inconclusive for clinical decision making. These aspects are addressed in the SmPC adequately.

3.6. Effects Table

Table 26. Effects Table for Ozawave (data cut-off: 26/03/2015 [1], 18/04/2015 [2]).

Effect	Short Description	Unit	Treatment	Control	Uncertainties/ Strength of evidence	Ref.
Favourable Effects						
ESS	change in ESS score at V6 corrected for baseline	points (SD)	-5.52 (4.41)	-2.75 (5.90)	**SoE**: LSmean difference (95% CI) -2.6 (-3.9 to -1.4), vs placebo p<0.001 (PE) Supported by ESS R1/R2 Response, CGIc and PGOE **Un**: A difference score of 3 points is considered clinically relevant Not supported by sleep diaries, OSleR	(1)
ESS	change in ESS score at V6 corrected for baseline	points (SD)	-6.3 (4.5)	-3.6 (5.5)	**SoE**: LSmean difference (95% CI) -2.8 (-4.0 to -1.5), vs placebo p<0.001 (PE) Supported by R1/R2 Response, CGIc and PGOE **Un**: A difference score of 3 points is considered clinically relevant Not supported by sleep diaries, OSleR	(2)
OSleR	change in sleep latency at V6 corrected for baseline	g. mean	1.442	1.219	**Un** vs placebo nominal p=0.075	(1)
		g.mean	1.65	1.39	**Un** vs placebo nominal p=0.167	(2)
Unfavourable Effects						
Headache	Incidence of treatment-related cases	%	9.6	10.6	The incidence rate was higher in pitolisant (12.4%) during OL period	(3)

Effect	Short Description	Unit	Treatment	Control	Uncertainties/ Strength of evidence	Ref.
Insomnia	Incidence of treatment-related cases	%	7.3	4.0		(3)
Nausea	Incidence of treatment-related cases	%	3.2	1.3		(3)
Abdominal Pain	Incidence of treatment-related cases	%	2.3	0.7		(3)

Abbreviations: CGIc= Clinician Global Impression of change, DB=Double Blind, ESS= Epworth Sleepiness Scale, ESS R1 Response = ESS≤ 10, ESS R2 Response = ESS ≤ 10 or ESS improvement ≥ 3, g.mean = geometric mean, OL=Open Label, OSleR= Oxford Sleep Resistance Test, PE= Primary Endpoint, PGOE= Patient's Global Opinion of Effect, SoE= strength of evidence, Un= uncertainty
Notes: (1) , (2) , (3) In the double-blind, placebo-controlled OSA studies HAROSA I/II/Pooled studies

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

Pitolisant treatment resulted in a statistically significant reduction in EDS as measured on the ESS score in both main studies. Regarding the ESS, a difference of at least 3 points in ESS score is considered a clinically relevant difference for EDS. In HAROSA-I and II, the difference in ESS compared to placebo was -2.6 and -2.8, respectively. Moreover, an effect of pitolisant in any of the objective secondary endpoints, and more specifically, the maintenance of wakefulness was not shown in neither one of the studies. Additional data provided by the Applicant has indicated that the pooled analyses can be considered supportive; however, these data also show a mean improvement on ESS of less than 3 points.

Preliminary results of the recently completed HAROSA-III study, evaluating 40 mg of pitolisant in patients either on or off concomitant CPAP treatment, indicate consistency with the results obtained in the HAROSA-I/II studies.

To support the clinical relevance of observed effect based on the totality of evidence, the efficacy and safety of pitolisant as observed in HAROSA-I/II is compared against to that of solriamfetol (Sunosi®). The results on the ESS with pitolisant fall within the range of ESS scores observed with solriamfetol.

Consistency of effect has been further substantiated by subgroup analyses, which indicate that the effect of pitolisant appears consistent across the subgroups.

A discussion on extrapolation of results obtained under nCPAP in HAROSA-I to concomitant use of pitolisant with other primary OSA therapies was requested as the proposed indication does not define a specific combination. Pitolisant is a symptomatic treatment of EDS, and its mechanism of action is not expected to differ when other types of primary OSA therapy are used.

The patients in HAROSA II did not receive any other primary OSA therapy as per exclusion criteria. This goes against recommendations of OSA treatment guidelines, where alternatives to nCPAP should be considered when nCPAP cannot be used. It remains unclear whether there is an increased risk of cardiovascular events or mortality when the underlying OSA remains untreated, as studies so far have shown conflicting results. There were at least two deaths (P0909-53-024 & one subject in P15-13) that occurred in the group of subjects not receiving any kind of primary OSA treatment. In these cases, the cause of death was considered related to the severe underlying OSA that was untreated.

The Applicant has proposed to restrict the indication without primary OSA therapy to the subgroup who cannot tolerate this and that this patient decision should be regularly rechallenged. Concomitant use of pitolisant with primary OSA therapy should still be considered the standard, however, it is acknowledged

that OSA subpopulation who cannot tolerate OSA therapy exists. The HAROSA-II study has shown that pitolisant can reduce EDS (as measured by ESS) in this patient population.

However, it is again emphasized that pitolisant is intended as a symptomatic treatment for EDS, and not a replacement for primary OSA therapy. Thus, there is uncertainty whether patients will no longer seek primary OSA therapy when a pharmacological treatment has become available for their EDS. By restricting the indication to patients who cannot tolerate primary OSA therapy, it is implied that patients should have first attempted OSA treatment prior to starting with pitolisant (regardless of their OSA severity).

As stated previously, the cardiovascular risk with untreated OSA cannot fully be excluded. Hence, it is considered important that patients without primary OSA therapy will be periodically re-challenged on this matter. Moreover, European treatment guidelines still recommend primary OSA therapy, regardless of OSA severity.

Taken together, the use of pitolisant in patients who cannot tolerate primary OSA therapy can be accepted, provided that patients are informed of the risks associated with not treating the underlying disease and that primary OSA therapy should be regularly re-challenged. The favorable effects of pitolisant used concomitantly with primary OSA therapy were never questioned. Therefore, the indication is worded as such to adequately reflect the target population in a clear and concise manner.

The overall safety profile of subjects in OSA studies, who received pitolisant during the double-blind placebo-controlled period, was comparable to the safety profile of those patients in All indications pooled data and safety profile of Wakix. The most common treatment-related TEAEs (>2%) during double-blind placebo-controlled all OSA studies were headache, insomnia, nausea and abdominal pain. Thus the safety profile of pitolisant is acceptable.

The remaining uncertainties are mostly due to lack of data (in females, normal weight and use during pregnancy) or methodological (non-OSA indications are not analysed separately, missing data in the analysis of laboratory findings).

3.7.2. Balance of benefits and risks

Pitolisant was shown to be efficacious to reduce EDS in patients with OSA. Efficacy and safety of pitolisant was evaluated in patient subpopulations either taking concomitant primary OSA therapy or those who did not, as they could not tolerate it. The indication of Ozawade has been revised to reflect this target population explicitly.

Furthermore, it is stated in SmPC section 4.2 that Ozawade is not a therapy for the underlying airway obstruction and that primary OSA therapy should be maintained or periodically rechallenged in patients not tolerating it.

The uncertainties on unfavourable effects are addressed in SmPC adequately.

Overall, it can be concluded that the benefits outweigh the risks for pitolisant for the improvement of wakefulness and reduction of excessive daytime sleepiness in OSA.

3.7.3. Additional considerations on the benefit-risk balance

N/A

3.8. Conclusions

The overall B/R of Ozawade is positive.

4. Recommendations

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the benefit-risk balance of Ozawade is favourable in the following indication:

Ozawade is indicated to improve wakefulness and reduce excessive daytime sleepiness (EDS) in adult patients with obstructive sleep apnea (OSA) whose EDS has not been satisfactorily treated by, or who have not tolerated, OSA primary therapy, such as continuous positive airway pressure (CPAP).

The CHMP therefore recommends the granting of the marketing authorisation subject to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal product subject to restricted medical prescription.

Other conditions and requirements of the marketing authorisation

Periodic Safety Update Reports

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

Risk Management Plan (RMP)

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

Obligation to conduct post-authorisation measures

NA

New Active Substance Status

The CHMP, based on the available data, considers that pitolisant is not a new active substance, as it is a constituent of a medicinal product previously authorised within the European Union. Pitolisant is contained in the marketing authorisation Wakix which was authorised in the European Union in in 2016.

Additional Data exclusivity /Marketing protection

Furthermore, the CHMP reviewed the data submitted by the applicant, taking into account the provisions of Article 14(11) of Regulation (EC) No 726/2004, and considers that the new therapeutic indication brings significant clinical benefit in comparison with existing therapies.

Appendix

1. CHMP AR on the novelty of the indication/significant clinical benefit in comparison with existing therapies