EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

19 November 2015
EMA/828546/2015
Committee for Medicinal Products for Human Use (CHMP)

# Assessment report

## Wakix

International non-proprietary name: pitolisant

Procedure No. EMEA/H/C/002616/0000

## Note

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

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# List of abbreviations

| | |
|---|---|
| **%CV** | Coefficient of Variation |
| **ADME** | Absorption, Distribution, Metabolism and Excretion |
| **AE** | Adverse Event |
| **ANCOVA** | Analysis of covariance |
| **ANOVA** | Analysis of variance |
| **AUC** | Area Under the Curve |
| **BF2.649** | Pitolisant |
| **BOCF** | Baseline Observation Carried Forward |
| **CGI** | Clinical Global Impression |
| **CGI-C** | Clinical Global Impression of Change |
| **CGI-S** | Clinical Global Impression of Severity |
| **CHMP** | Committee for Medicinal Products for Human Use (European Medicines Agency) |
| **$C_{max}$** | The peak plasma concentration of a drug after administration |
| **$C_{min}$** | The lowest (trough) concentration that a drug reaches before the next dose is administered |
| **CNS** | Central Nervous System |
| **CSR** | Clinical Study Report |
| **DCR** | Daily Cataplexy Rate |
| **DDI** | Drug-Drug Interaction |
| **DCS** | Differential Scanning Calorimetry |
| **EDS** | Excessive daytime sleepiness |
| **EIT** | Extended Intend to Treat |
| **EMA** | European Medicines Agency |
| **ESS** | Epworth Sleepiness Scale |
| **ESSB** | ESS Baseline value |
| **ESSF** | ESS Final value |
| **EU** | European Union |
| **FDA** | US Food and Drug Administration |
| **FUA** | Follow-up advice |
| **GCP** | Good Clinical Practice |
| **ITT** | Intention to Treat (population) |
| **kg** | Kilogram |
| **LOCF** | Last Observation Carried Forward |
| **mg** | Milligram |
| **Ml** | Millilitre |
| **MSLT** | Multiple Sleep Latency Test |
| **MWT** | Maintenance of Wakefulness Test |
| **ng** | Nanogram |
| **OR** | Odds Ratio |
| **PD** | Pharmacodynamics |
| **PDCO** | Paediatric Committee (European Medicines Agency) |
| **PIP** | Paediatric Investigation Plan |
| **PK** | Pharmacokinetics |
| **PP** | Per protocol (population) |
| **QD** | Quaque die (every day) |
| **REM** | Rapid eye movement |

| | |
|---|---|
| **SA** | Scientific Advice |
| **SART** | Sustained Attention to Response Task |
| **SmPC or SPC** | Summary of Product Characteristics |
| **SWS** | Slow wave sleep |
| **$t_{max}$** | Time to reach $C_{max}$ |
| **TGA** | Thermogravimetry Analysis |
| **UGT** | UDP-glucuronosyltransferase |
| **US or USA** | United States of America |
| **WCR** | Weekly Cataplexy Rate |
| **XRPD** | X-ray powder diffraction |

# 1. Background information on the procedure

## *1.1. Submission of the dossier*

The applicant Bioprojet Pharma submitted on 7 May 2014 an application for Marketing Authorisation to the European Medicines Agency (EMA) for Wakix, through the centralised procedure falling within the Article 3(1) and point 4 of Annex of Regulation (EC) No 726/2004. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 21 July 2011.

Wakix was designated as an orphan medicinal product EU/3/07/459 on 10 July 2007, in the following indication: treatment of narcolepsy.

Following the CHMP positive opinion on this marketing authorisation, the Committee for Orphan Medicinal Products (COMP) reviewed the designation of Wakix as an orphan medicinal product in the approved indication. The outcome of the COMP review can be found on the Agency's website: ema.europa.eu/Find medicine/Human medicines/Rare disease designations.

The applicant applied for the following indication: treatment of narcolepsy with or without cataplexy.

**The legal basis for this application refers to:**

Article 8.3 of Directive 2001/83/EC - complete and independent application. The applicant indicated that pitolisant was considered to be a new active substance.

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 tests or studies.

***Information on Paediatric requirements***

Pursuant to Article 7 of Regulation (EC) No 1901/2006, the application included an EMA Decision P0200/2013 on the agreement of a paediatric investigation plan (PIP). The PIP includes a waiver for all subsets of the paediatric population from birth to less than 6 years of age.

At the time of submission of the application, the PIP 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.

**New active Substance status**

The applicant requested the active substance pitolisant hydrochloride contained in the above medicinal product to be considered as a new active substance in itself, as the applicant claimed that it is not a

constituent of a product previously authorised within the Union.

***Scientific Advice***

The applicant received Scientific Advice from the CHMP/COMP on 20 of September 2007 for the development of pitolisant for the treatment of excessive daytime sleepiness in narcolepsy, Parkinson disease and obstructive sleep apnoea (OSA), with follow-up advices (FUA) adopted by CHMP/COMP on February 2010, September 2010 and November 2011. The Scientific Advice pertained to non-clinical and clinical aspects of the dossier.

***Licensing status***

The product was not licensed in any country at the time of submission of the application.

## *1.2. Steps taken for the assessment of the product*

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

Rapporteur: Joseph Emmerich Co-Rapporteur: Greg Markey

- The application was received by the EMA on 7 May 2014.
- The procedure started on 28 May 2014.
- The Rapporteur's first Assessment Report was circulated to all CHMP members on 18 August 2014. The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on 15 August 2014.
- PRAC assessment overview, adopted by PRAC on 11 September 2015.
- During the meeting on 25 September 2014, the CHMP agreed on the consolidated List of Questions to be sent to the applicant. The final consolidated List of Questions was sent to the applicant on 29 September 2015.
- The applicant submitted the responses to the CHMP consolidated List of Questions on 18 March 2015.
- The Rapporteurs circulated the Joint Assessment Report on the applicant’s responses to the List of Questions to all CHMP members on 24 April 2015.
- PRAC RMP Advice and assessment overview, adopted on 7 May 2015
- During the CHMP meeting on 21 May 2015, the CHMP agreed on a List of Outstanding Issues to be addressed in writing by the applicant.
- The applicant submitted the responses to the CHMP List of Outstanding Issues on 21 September 2015.
- The Rapporteurs circulated the Joint Assessment Report on the applicant’s responses to the List of outstanding issues to all CHMP members on 29 September 2015.
- PRAC RMP Advice and assessment overview, adopted on 8 October 2015.
- During the CHMP meeting on 22 October 2015, the CHMP agreed on a second List of Outstanding Issues to be addressed in writing by the applicant.
- The applicant submitted the responses to the second CHMP List of Outstanding Issues on 28

October 2015.

- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the second List of outstanding issues to all CHMP members on 5 November 2015.
- PRAC RMP Advice and assessment overview, adopted on 6 November 2015.
- During the meeting on 19 November 2015, 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 Wakix.

# 2. Scientific discussion

## *2.1. Introduction*

**Problem statement**

Narcolepsy is a rare and disabling disorder affecting the sleep and wakefulness regulation. A deficit of hypocretin (orexin), a wake stimulating peptide produced by thalamic nuclei, is hypothesized to be the key underlying mechanism. The two cardinal clinical features of narcolepsy are excessive daytime sleepiness (EDS) and cataplexy. It is a chronic and often extremely incapacitating disease with negative impact on the quality of life of affected patients, interfering with every aspect of life, in work and social settings. The prevalence of narcolepsy with cataplexy is estimated to be between 25 and 50 per 100,000 people.

Treatment strategies rely on relief of symptoms. With EDS being the most prevalent and the most problematic for the patients, most of the treatments target this particular symptom. Stimulant medications, by increasing monoaminergic activity, have been the milestone of therapy for many decades. Modafinil is approved for the treatment of excessive sleepiness related to narcolepsy, but its mechanism of action is not fully understood. It is considered as the first line pharmacological treatment for EDS, but there is discrepancy on its effect on cataplexy. Amphetamines and methylphenidate, acting on dopamine and norepinephrine receptors, have been commonly used in this indication. However, these medications can have serious side effects, mostly on cardiovascular and nervous systems (hypertension, tachycardia, anxiety, depression, mania, motor tics, etc.) and could lead to abuse disorders and weight loss. Cataplexy is treated by sodium oxybate and antidepressants. Sodium oxybate is also approved for the treatment of EDS in narcolepsy but it is associated with significant abuse, dependence and withdrawal symptoms.

**About the product**

Histaminergic neurons are mainly located in the posterior hypothalamus. They play a role in arousal mechanisms. It has been shown that histamine H3 receptors (H3R), only activated by inverse agonists, were able to promote activation of cerebral histamine neurons.

Pitolisant is an orally active antagonist/inverse agonist of the human histamine H3 receptor. It works by enhancing the histaminergic transmissions in brain, acetylcholine release in prefrontal cortex and hippocampus and dopamine release in prefrontal cortex but not in striatum.

## *2.2. Quality aspects*

### 2.2.1. Introduction

The finished product is presented as film-coated tablets containing 4.5 mg of pitolisant (equivalent to 5 mg of pitolisant hydrochloride) and 18 mg of pitolisant (equivalent to 20 mg of pitolisant hydrochloride) as active substance.

Other ingredients are:

Tablet core: microcrystalline cellulose, crospovidone Type A, talc, magnesium stearate, colloidal anhydrous silica.

Coating: polyvinyl alcohol, titanium dioxide (E171), macrogol 3350, and talc.

The product is available in high density polyethylene (HDPE) bottle with a tamper evident, child-resistant, polypropylene screw cap fitted with silica gel desiccant.

### 2.2.2. Active Substance

#### *General information*

The chemical name of pitolisant hydrochloride is 1-{3-[3-(4-chlorophenyl)propoxy]propyl}piperidine, hydrochloride and has the following structure:

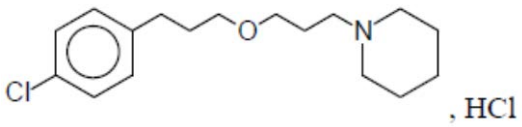



**Figure 1:** Structural Formula of BF2.649

Pitolisant is a *w*hite or almost white crystalline powder. Hygroscopicity was confirmed by dynamic vapor sorption studies and therefore water is controlled in the specifications, the active substance is very soluble in water, ethanol and methylene chloride, freely soluble in acetone, and practically insoluble in cyclohexane. The active substance is the crystalline pitolisant hydrochloride obtained as a stable polymorphic form. A polymorphism study was carried out using methods such as XRPD, DSC, TGA as well as thermal treatments and milling. Pitolisant has a non - chiral molecular structure. Therefore, the active substance does not exhibit stereoisomerism.

The information on the active substance is provided according to the Active Substance Master File (ASMF) procedure.

#### *Manufacture, characterisation and process controls*

The active substance is provided by two commercial suppliers; the quality of the AS from both is considered as equivalent. Only one supplier will be used for commercial batches.

The active substance pitolisant hydrochloride is obtained in two reaction steps followed by a salt formation and a recrystallization. Two starting materials are used. One of the starting materials proposed is commercially available well defined with acceptable specifications. Regarding the other starting material, the information provided showed that genotoxic compounds were involved in the

manufacturing process and therefore this step is considered as critical and should be part of the manufacturing process performed under GMP. Additionally, the proposed controlled strategy was not considered satisfactory since the starting material specifications did not include tests and acceptance criteria for potential genotoxic impurities. Therefore, the redefinition of this starting material was requested. The ASMFH agreed to redefine this stating material and update the ASMF accordingly. However, since setting a new GMP synthesis with validation batches is a long process; this issue will be handled as post approval change in June 2016. The ASMFH committed to stop manufacturing of new batches of API from current non GMP starting material. There is no immediate concern with the quality of the product as future batches of finished product will be manufactured with active substance manufactured following redefinition. This was considered satisfactory.

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 characterisation of the active substance and its impurities are in accordance with the EU guideline on chemistry of new active substances. Potential and actual impurities were well discussed with regards to their origin and characterised.

An exhaustive discussion on potential impurities was provided. The impurities were mainly controlled in the active substance specifications or the absence of control in routine was properly justified by experimental results and spiking experiments.

All syntheses, from early laboratory research up to current process have been run with the same general scheme.

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 fiberboard drum. Specifications of the polyethylene bags have been provided and include an identification test by IR. The polyethylene bags comply with EU foodstuffs regulation Directive 2002/72/EC).

Detailed information on the manufacturing of the active substance has been provided in the restricted part of the ASMF and it was considered satisfactory.

## *Specification*

The active substance specification includes tests for appearance, solubility (Ph Eur), identification (IR, melting point, and LC), identification of chlorides (Ph Eur), appearance of solution (Ph Eur), pH (Ph Eur), water content (Ph Eur), residue of ignition (Ph Eur), heavy metals (Ph Eur), related substances (LC-UV), residual solvents (GC), assay (LC), and particle size (laser diffraction).

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 testing has been presented.

Batch analysis data for commercial scale batches of the active substance were provided. The results are within the specifications and consistent from batch to batch.

## *Stability*

Stability data on three commercial scale batches of the active substance from the proposed manufacturer stored in the intended commercial package for 24 months under long term conditions at

25ºC / 60% RH and for up to 6 months under accelerated conditions at 40ºC / 75% RH according to the ICH guidelines were provided.

The analytical methods used were the same as for release and were stability indicating.

No significant changes have been observed up to 24 months in any parameters tested.

Results on stress conditions including exposure to neutral, acid, basic, oxidative conditions, heating and high intensity UV light (solid and solution) were also provided on one commercial scale batch.

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 24 months in the proposed container.

## 2.2.3. Finished Medicinal Product

### *Description of the product and Pharmaceutical development*

The finished product is presented as film-coated tablets dosed respectively at 4.5 mg - White, round, biconvex film-coated tablet of approximately 3.7 mm in diameter engraved 5 on one side - and 18 mg - White, round, biconvex film-coated tablet of approximately 7.5 mm in diameter engraved 20 on one side - of active ingredient with the same qualitative and relative quantitative composition of excipients.

The aim of pharmaceutical development was to develop an immediate release solid dosage form to achieve the following objectives:

- An oral dosage form suitable for administration of approximately less than 20% concentration of the tablet weight with quantity of excipients as low as possible to obtain a tablet as small as possible.

- Using well known and compatible excipients providing satisfactory chemical stability of the active substance

- Leading to the objective of mean percent of active substance dissolved of 100% at 30 minutes with slight inter and intra batch variation

- A film-coating was applied to mask the bitter taste of the drug substance.

The choice of dosage form took into account the following characteristics 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 leading to the main identified degradation product, i.e. N-oxide derivative, and has a very strong and prolonged bitter taste.

The pharmaceutical form intended for commercial use is an immediate release film-coated tablet which could be divided into four equal parts by applying a pressure to the centre of the tablet placed on a flat surface. One quarter of a tablet contains a dose of 4.5 mg of pitolisant. The recommended dose is 18 mg once-a-day. However, according to personal variations in sensitivity to the daytime waking and nocturnal insomnia of the patients under treatment, the dose could be reduced. .

However, during the assessment of the dossier, the CHMP considered that the need for the patient to break the 18 mg cross-scored film-coated tablet (especially into quarters) to obtain the required dose was not acceptable. Additionally searching in the bottle, for subsequent doses, was found unreasonable to remaining quarters in amongst the whole tablets. Therefore, a 4.5 mg strength was developed and consequently the format of tablets was changed from cross-scored to biconvex tablets which is the pharmaceutical form intended to be marketed.

All excipients are well known and their quality is compliant with Ph. Eur standards with the exception of film-coating agent which is controlled by an in-house specifications and compatible for use in pharmaceuticals. Standard ingredients in tablet formulations. The concentration of each excipient in the tablet core lies within the usual range in such a dosage form. In order to efficiently mask the bitter taste of the active substance, the film-coating agent, Opadry, is applied. There are no novel excipients used in the finished product formulation. The list of excipients is included in section 6.1 of the SmPC.

The manufacturing process by direct tabletting has remained unchanged throughout clinical development and the film-coating process was introduced at start of phase III The film-coated tablets are packed in plastic bottle (HDPE) with a tamper evident, child-resistant polypropylene (PP) screw cap fitted with a desiccant. The plastic material complies with the EU regulations on food contact applications and Ph.Eur. 3.1.3 “Polyolefines” and Ph.Eur. 3.2.2 “Plastic containers and closures for pharmaceutical use”.

## *Manufacture of the product and process controls*

Wakix is manufactured by direct compression and film-coating of the core tablets

The manufacturing process consists of six main steps: blending 1, blending 2, compression, preparation of coating suspension, coating and packaging. The process is considered to be a standard manufacturing process.

Critical steps of the process have been identified and are considered as well controlled.

Major steps of the manufacturing process (blending, compression, coating suspension, film coating and packaging) have been validated by a number of studies. 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.

## *Product specification*

The finished product release specifications include appropriate tests for this kind of dosage form: description, identification (LC, UV), average mass (Ph Eur), uniformity of mass (Ph Eur), uniformity of dosage units (Ph Eur), water content (Ph Eur), disintegration time (Ph Eur), dissolution test (Ph Eur), assay (HPLC), impurities (HPLC, GC), microbiological quality (Ph Eur). The product release and shelf life specifications and acceptance criteria are in line with the current relevant guidelines.

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

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

Batch analysis results are provided for three commercial batches per strength confirming the consistency of the manufacturing process and its ability to manufacture to the intended product specification.

## *Stability of the product*

Stability data of three 18 mg strength, cross-scored film-coated tablets commercial scale batches of finished product from two manufacturers stored under long term conditions for 36 and 18 months

respectively at 25ºC / 60% RH, and intermediate conditions for up 12 months at 30°C / 75% RH for one manufacturer and for up to 6 months under accelerated conditions at 40ºC / 75% RH for both manufacturers according to the ICH guidelines were provided. The batches of the medicinal product are identical to those proposed for marketing and were packed in the primary packaging proposed for marketing.

Additional stability studies have been performed on three 18 mg dosage strength biconvex film coated tablets commercial scale batches stored under long term conditions for 6 months at 25ºC / 60% RH, and intermediate conditions at 30°C / 75% RH and for up to 6 months under accelerated conditions at 40ºC / 75% RH according to the ICH guidelines. The batches of the medicinal product are identical to those proposed for marketing and were packed in the primary packaging proposed for marketing.

Regarding the 18 mg strength, cross-scored film-coated tablets, no significant change of the physical characteristics change is observed.

Regarding the 18 mg strength, stability studies have been performed as well on three commercial scale batches of pitolisant 4.5 mg strength, stored for 6 months at 25°C / 60% RH, 30°C / 75% RH, and 40°C / 75% RH. A trend is observed for the main degradation product at 40°C/75% RH. This trend is similar to the observed results for the 18 mg strength. The absence of special storage conditions is accepted, but the shelf life with the current provided data justify a shorter than the shelf life of the 18 mg strength.

The analytical methods used were the same as for release and were stability-indicating.

A forced degradation study on one commercial scale batch was performed under the following stress conditions: thermal stress for 1 week at 50°C, acidic conditions in HCl 0.1 M at 50°C for 24 hours, alkaline conditions in NaOH 0.1 M at 50°C for 24 hours, oxidative stress in $H_2O_2$ 0.9 % m/v (3 vol) at room temperature for 24 hours.

An in-use stability study has been performed on the pitolisant 18 mg, biconvex film coated tablets, and on the three commercial scale batches of pitolisant 4.5 mg, film coated tablet. After one month daily opening, pitolisant 18 mg and 4.5 mg, film-coated tablets packed in 20-mL bottle (HDPE) with child resistant, tamper evident polypropylene (PP) closure fitted with 2.4-G desiccant (30 tablets per bottle) and stored under 30°C / 75% RH showed no change of physical nor chemical characteristics of the product.

In addition, one batch was exposed to light as defined in the ICH Guideline on Photostability Testing of New Drug Substances and Products.

No significant change of the physical characteristics was observed, i.e. appearance, disintegration time, average mass, water content, hardness, dissolution profile which remain far below the acceptance criteria.

Based on stability data provided, a shelf life of 30 months without any special storage conditions for the 18 mg strength and 12 months without any special storage conditions for the 4.5 mg strength are acceptable at the time of the authorisation.

### *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.

At the time of the CHMP opinion, there were a number of minor unresolved quality issues having no impact on the Benefit/Risk ratio of the product.

### 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(s) 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:

- To redefine the starting material and update the ASMF accordingly.

## *2.3. Non-clinical aspects*

### 2.3.1. Introduction

The nonclinical pharmacology programme for pitolisant consisted of *in vi*tro assays and *in vivo* pharmacodynamic studies. Pharmacokinetic studies were performed to determine ADME and drug-drug interaction potential. The nonclinical toxicology programme consisted of acute and repeated dose studies, genotoxicity assays, carcinogenicity studies, and the evaluation of reproductive and developmental toxicity. Abuse liability studies were also conducted.

All pivotal toxicology studies were performed in accordance with GLP.

### 2.3.2. Pharmacology

***Primary pharmacodynamic studies***

Pitolisant binds human histamine 3 receptor (H3R) with Ki values ranging from 1.0 to 2.4 nM (corresponding to IC50 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 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 EC50 and Emax values reaching 1.5 nM and 25%, respectively.

Pitolisant was not specific for H3R over sigma $\sigma_1$ and $\sigma_2$ 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 EC50 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 IC50 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 IC50 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 ED50 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 $\geqslant$10 mg/kg. In orexin KO mice, the results suggested also 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 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 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.

***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 hypothesized 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 generalized clonic seizures in epileptic subjects. In addition, pitolisant was not active on generalized 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 normalized 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.

***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 anaesthetized 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-anaesthetized 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 compound 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

In rats 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 by CYP3A4 in gut In Cynomolgus monkeys, the oral bioavailability of unchanged pitolisant in plasma was 27% and nearly 100% when total [$^{14}$C] was considered.

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 significant ones in the liver and kidney. Distribution to melanin containing structures (skin, uveal tract) was also reported in partially pigmented rats. In male Cynomolgus monkeys, high radioactivity levels were identified in GI tract, liver, kidneys, seminal vesicles and prostate. In both rats and monkeys receiving [$^{14}$C]-pitolisant i.v., the apparent volume of distribution of pitolisant at steady state was approximately 10-fold greater than total body water, indicating extensive tissue distribution. Pitolisant was highly bound (above 88%) to serum protein in human, monkey, dog, rat and mouse; over the concentration range of 100 nM to 1 µM, the main phase I human metabolite BP2.951 exhibited moderate serum protein binding compared to pitolisant.

Pitolisant crosses the placenta and was found in milk in rats.

*In vitro* metabolism studies of pitolisant using microsomes and hepatocytes, have shown that the two major non-conjugated metabolites were BP2.941 and BP2.951 in monkeys and humans. Other oxidized metabolites of pitolisant such as BP1.2525 and BP1.2526 were present but to a minor extent. In contrast, the drug metabolism in rats was different, wherein BP1.2526 presents in very low levels in humans, being the major non-conjugated metabolite whereas BP2.951 and BP2.941 found in minor quantities. Pharmacological activity of the main metabolites over human H3 receptors revealed that only BP1.2526 and BP1.2525 at a lesser extent have an affinity towards human H3 receptor.

In rats, main metabolites in these samples are mostly conjugated entities; however non-conjugated metabolite such as BP1.2526 was also abundant and in a lesser extent BP1.2525 in tested matrices. From the comparison of metabolites formed *in vivo* in Cynomolgus monkeys and in humans, the applicant did conclude that Cynomolgus monkeys could be used as the non-rodent species for toxicity studies. Nevertheless, it should be noted that the metabolite BP1.8054, a glycine conjugate of a phase I metabolite, was only detected in humans and neither in monkeys nor rats. Therefore the toxicity species were not considered fully validated and the applicant was asked to submit additional studies to characterize this metabolite toxicity. These studies were performed and data submitted to the authorities (see Toxicology section 2.3.4).

Excretion/elimination was characterized 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 with a majority of the radioactivity in urine and faeces (98.4 and 92.6%, 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.)).

Following oral and intravenous administration of [$^{14}$C]-pitolisant to monkeys, the majority of the dose was recovered in urine (69.9% and 63.3%, respectively). 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.

## 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.

Table 1 below shows major findings observed in repeat-dose toxicology studies.

**Table 1: Repeat-dose toxicity studies**

| Species/Sex/ Number/ Group/ (Study ID) | Route of administration Dose (mg/kg) Duration | NOAEL (mg/kg) | Major findings | GLP |
|---|---|---|---|---|
| Mouse CB6F1-nonTgrasH2 wild type (Main: 10; TK: 20) | Oral 30, 75, 100 4 weeks | 75 | - No mortality.<br><u>At 75 mg/kg/d</u><br>- Hypoactivity, staggering gait (in M).<br>- ↑ Liver weight<br>- ↑ cholesterol + triglycerides.<br><u>At 100 mg/kg/d</u><br>- Slightly ↑cholesterol and triglycerides levels<br>- ↑ liver weights + minimal centrilobular hypertrophy of hepatocytes in M.<br>- Hypoactivity (higher frequency in M), clonic convulsions in M (5/10);<br>- Staggering gait + loss of balance + ptyalism in M (only at 100 mg/kg). | Yes |
| Rat Sprague-Dawley (Main: 10; Recovery: 10;TK:11) | Oral 5, 30, 150/100/75 13 weeks (+ 3 weeks recovery) | 30 | <u>At 30 mg/kg</u>/d<br>- Vocalisation + aggressive behaviour (1/10).<br><u>At 75 mg/kg/d</u><br>- Mortality<br>- Vocalisation, aggressive behaviour (5/20 in M, 4/20 in F), salivation, trembling (2/20 in M, 5/20 in F), dyspnoea, uncontrolled movements (4/20 in M, 6/20 in F), prostration (1/20 in M, 4/20 in F), excitation (4/20 in M, 11/20 in F), yellowish faeces, polyuria.<br>- ↑ AST<br>- ↑ liver weight<br>- Non reversible lipoid pneumonia foci, haemorrhagic area, oedema in lungs | Yes |

| Species/Sex/ Number/ Group/ (Study ID) | Route of administration Dose (mg/kg) Duration | NOAEL (mg/kg) | Major findings | GLP |
|---|---|---|---|---|
| Rat Sprague-Dawley (Main: 20, recovery 5) | Oral 5, 30, 75/60 6 months (+ 4 weeks recovery) | 30 | At 30 mg/kg/d<br>- Salivation<br>- ↑ Liver weight (relative)<br>At 75 mg/kg/d<br>- Mortality in all animals<br>At 60 mg/kg/d<br>- Convulsions (18/25 in M, 16/25 in F), salivation, tremors, subdued behaviour and abnormal gait, piloerection, pupil dilatation, dyspnoea noisy breathing.<br>- Weight: ↓ spleen and thymus for M only, ↑ liver, ↑ kidney, ↑ adrenals.<br>- Lungs: pale foci (3/18 in F), non-reversible focal increased alveolar macrophages mostly in F (15/18);<br>- Adrenals: diffuse cortical hypertrophy in F (6/18);<br>- Duodenum: mucosal alterations in M (9/17) and F (7/18);<br>- Stomach: ulceration/inflammation in M (2/17);<br>- Liver: hepatocellular alterations in M (15/17) and F (13/18), scattered vacuolation in M (7/17). | Yes |
| Cynomolgus monkey/ macaca fascicularis (4 +2 for recovery) | Oral 5, 12 or 30 13 weeks + Recovery 4 weeks | 12 | - At 12 mg/kg/d<br>- Emesis in 2M.<br>- Slight ↑ in AST/GOT and ALT/GPT<br>- At 30 mg/kg/d<br>- Tremors (M, F), salivation (M, F), clonic convulsions in 1M, emesis-vomit (M, F)<br>- Slight ↑ in AST/GOT, ALT/GPT and triglycerides.<br>*Conclusion*:<br>All clinical signs were reversible. | Yes |
| Cynomolgus monkey/ macaca fascicularis (4 + 2 for recovery) | Oral 5, 12 or 30 9 months + Recovery 4 weeks | 12 | - At 30 mg/kg/d<br>- Tremors (1/4 in F and M), agitation (1/4 in F), unsteady gait (3/4 in M and 1/4 in F); convulsions (3/4 in M and 1/4 in F).<br>*Conclusion*:<br>All clinical signs were reversible. | Yes |

M: male F: female

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.

***Genotoxicity***

Submitted genotoxicity studies are summarised in the table below.

**Table 2: Summary of genotoxicity studies with Pitolisant, BP2.951 and BP1.2526 (metabolites)**

| Type of test | Test system | Test compound/Concentrations (or range) / Metabolising system / Route of administration | Results | GLP |
|---|---|---|---|---|
| *In vitro* | | | | |
| Gene mutations in bacteria | *S.typhimurium* TA98, TA100, TA1535, TA1537, *E.coli* WP2uvrA (-S9 mix)<br>*S.typhimurium* TA98, TA100, TA102, TA1535, TA1537 (+S9 mix) | Pitolisant /-S9 mix activation<br>156.25, 312.5, 625, 1250 and 2500 µg/plate<br>Only up to 1250 µg/plate (+T) with *E.coli* WP2uvrA<br>Pitolisant /+S9 mix activation<br>39.06, 78.13, 156.25, 312.5, 625, 1250 and 2500 µg/plate (+T) | Negative | Yes |
| Gene mutations in bacteria | *S.typhimurium* TA98, TA100, TA102, TA1535, and TA1537. | BP2.951 +/-S9 mix activation<br>50, 150, 500, 1500 and 5000 µg/plate +/- *S9* | Negative | Yes |
| Gene mutations in bacteria | *S.typhimurium* TA98, TA100, TA102, TA1535 and TA1537. | BP1.2526 /-S9 mix activation<br>312.5, 625, 1250, 2500 and 5000 µg/plate<br>BP1.2526 /+S9 mix activation<br>39.06, 78.13,125.3, 312.5, 625, 1250, 2500 and 5000 µg/plate | Negative | Yes |
| Gene mutations and chromosome aberrations in mammalian cells | L5178Y TK+/- mouse lymphoma cells | Pitolisant +/-S9 mix activation<br>Exp 1: (4 hours): 2.5, 5.0, 10, 20, 40 and 55 µg/mL<br>Due to severe toxicity, a second experiment was conducted with a lower concentration range<br>Exp 2: (24 hours): 1.3, 2.5, 5.0, 10, 15 and 20 µg/mL | Negative | Yes |
| *In vivo* | | | | |
| Micronucleus assay in mice | Mouse Swiss (5M/5F)<br>Number of cell analyzed:<br>1000 polychromatic erythrocytes | Pitolisant<br>Single oral sub-lethal dose : 150 mg/kg<br>Bone marrow samples taken 24, 48h.<br>Positive control: cyclophosphamide<br>+ Evidence of exposure | Negative | Yes |
| Micronucleus assay in mice | Mouse Swiss (5M/5F)<br>Number of cell analyzed:<br>2000 polychromatic erythrocytes | Pitolisant<br>12.5, 25 and 50 mg/kg, p.o.<br>Two administrations 24 h apart<br>Bone marrow samples taken 24h after the second treatment.<br>Positive control: cyclophosphamide<br>+ Evidence of exposure | Negative | Yes |

T = toxicity

Pitolisant and two metabolites (BP1.2526, BP2.951) did not cause any gene mutation in Ames test in 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.

***Carcinogenicity***

Two carcinogenicity studies were conducted to evaluate the potential carcinogenicity of orally administered pitolisant in mice and rats. The design and major findings of each study are described in table 3.

**Table 3: Summary of carcinogenicity studies in rats and mice**

| Species(No) | Route Dose (mg/kg) Duration | NOAEL | Major findings | GLP |
|---|---|---|---|---|
| Rat Sprague-Dawley (60/sex/group) + TK (satellite) | Oral 5, 15, 30 105/106 weeks | MTD = 30 | Neoplastic lesions:<br>- No statistically significant neoplastic findings<br>Non neoplastic findings:<br>- Enlarged ears, kidneys and livers mostly in M (15 and 30 mg/kg).<br>- ↑ granulomas in the lungs in M (30 mg/kg).<br>- ↑ myeloid cell number in the bone marrow in M (30 mg/kg).<br>Clinical signs:<br>- Alopecia of abdomen (at all doses), ptyalism (in all animals at 30 mg/kg), clonic convulsions (mainly at 30 mg/kg), soiled urogenital region (15 and 30 mg/kg). | Yes |
| CB6F1 Tgras H2 mice (25/sex/group) + TK (satellite) | Oral 15, 30, 75 26 weeks | 75 | Neoplastic lesions:<br>- No statistically significant neoplastic findings<br>Non neoplastic findings:<br>- ↑ liver relative weight in M and F + hepatocellular hypertrophy (in all doses).<br>- Increased incidence of pale basophilic bodies in the testes (75 mg/kg)<br>Clinical signs:<br>- Hunched posture, hypoactivity (in all doses), dyspnoea (15 and 75 mg/kg), clonic convulsions (75 mg/kg). | Yes |

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, slight 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 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 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.

***Toxicokinetic data***

The results of the toxicokinetic evaluation of pitolisant and metabolite BP2.951 in the oral repeated dose toxicity studies are presented in table 4 below.

**Table 4: Overview of toxicokinetic data for pitolisant and metabolite BP2.951 in mice, rats and monkey and safety margins**

| **Species** Duration **[NOAEL] (mg/kg/day)** | **Product** | **Male** | | **Ratio compared with human* $C_{max}$/AUC (Male)** | **Female** | | **Ratio compared with human* $C_{max}$/AUC (Female)** |
|---|---|---|---|---|---|---|---|
| | | **$C_{max}$ (ng/ml)** | **$AUC_{(0-t)}$ (ng hr/ml)** | | **$C_{max}$ (ng/ml)** | **$AUC_{(0-t)}$ (ng hr/ml)** | |
| **Mouse** 4-week p.o. **[75]** | Pitolisant | 1705 | 8855 | **23/11** | 1744 | 5535 | **24/6.9** |
| | BP2.951 | 444 | 646 | **17/3.7** | 300 | 419 | **11.5/2.4** |
| **Rat** 6-month p.o. **[30]** | Pitolisant | 558 | 681 | **7.8/0.8** | 745 | 996 | **10.3/1.2** |
| | BP2.951 | 76 | 167 | **2.9/0.96** | 186 | 324 | **7.2/1.9** |
| **Monkey** 9-month p.o. **[12]** | Pitolisant | 81 | 375 | **1.1/0.4** | 72 | 318 | **1/0.4** |
| | BP2.951 | 405 | 1190 | **15.5/6.5** | 385 | 1120 | **14.8/6.5** |

* The steady state Cmax and $AUC_{0-t}$ used in the margin calculations for pitolisant were 72 ng/mL and 804 ng/mL*h, respectively at maximum therapeutic dose of 40 mg per day (study P04-06). For BP2.951, the Cmax and $AUC_{0-t}$ were 26 ng/mL and 173 ng/mL*h, respectively. These values were from the Study P-03-03 performed in humans following 40 mg daily dosing.

Regarding the metabolites, evidence of exposure of metabolites (BP2.951, BP1.2526, BP1.2525) were shown in mice, rats and monkeys. BP2.951, BP1.2526 were compared to pharmacokinetic parameters of pitolisant in humans at 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). Furthermore, the major glucuronide metabolite in human species was measured in monkey (9-month) samples leading to satisfying safety margins.

In regards to the toxicity mainly related to CNS effects (convulsions), the applicant argued that a safety margin based on $C_{max}$ is more relevant than based on AUC leading to safety margins around 25, 10 and 1 for mice, rats and monkeys, respectively (convulsions occur at around the $T_{max}$). However, it would be more reliable to have a statistically significant correlation between convulsions and the $C_{max}$ taking into account high levels of pitolisant and overall metabolites in any species. Nevertheless, the safety margin based upon the $C_{max}$ was still 1 for monkey. Whatever based on $C_{max}$ or AUC, there was no safety margin in monkey.

***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 route 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). Dependence potential of pitolisant was assessed in rats with morphine, cocaine or amphetamine as 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, 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, 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 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, the investigation of photosafety was not conducted.

## 2.3.5. Ecotoxicity / environmental risk assessment

The applicant has submitted an ERA based on the EMEA/CHMP/SWP/4447/00 guideline. For the Phase I PEC calculation, Fpen was refined based on the prevalence of narcolepsy in the European Union.

Pitolisant PEC surfacewater value is below the action limit of 0.01 µg/L and is not a PBT substance as log Kow does not exceed 4.5. Therefore pitolisant is not expected to pose a risk to the environment.

**Table 5 Summary of main study results**

| | | | |
|---|---|---|---|
| **Substance (INN / Invented Name): Pitolisant** | | | |
| **CAS-number (if available): 903576-44-3** | | | |
| ***PBT screening*** | | Result | **Conclusion** |
| *Bioaccumulation potential*- log $K_{ow}$ | OECD122 | 0.85 ±0.18 (at 25°C;pH 6.8) | Potential PBT - N |
| ***PBT-assessment*** | | | |
| **Parameter** | **Result relevant for conclusion** | | **Conclusion** |
| Bioaccumulation | log $K_{ow}$ | 0.85 | not B |
| **PBT-statement :** | The compound is not considered as PBT nor vPvB | | |
| ***Phase I*** | | | |
| **Calculation** | **Value** | **Unit** | **Conclusion** |
| PEC $_{surfacewater}$ , default or refined (e.g. prevalence, literature) | 0.009 µg/l | µg/L | > 0.01 threshold (N) |
| Other concerns (e.g. chemical class) | | | None |

## 2.3.6. Discussion on non-clinical aspects

Pitolisant is a potent histamine 3 receptor (H3R) antagonist/inverse agonist. The H3R was first characterized as an auto-receptor, regulating the electrical activity of histaminergic neurons as well as the synthesis and release of histamine. Histaminergic neurons are arranged in the tuberomamillary nucleus in the hypothalamus, from which they send highly divergent axons to the brain and the spinal cord. These neurons are mainly active during day, almost silent during night and their main function is to promote wakefulness, attention and cognitive functions. Hence, pharmacological blockade of the H3-autoreceptor enhances histaminergic neuron activity and results in promotion of wakefulness and pro-cognitive effects.

*In vivo* studies in wild-type and orexin KO mice, and in cats showed that pitolisant increased the duration of waking at the expense of SWS and PS with corroborating EEG changes at ≥10 mg/kg (p.o.), thereby supporting a proof-of-concept for its use in narcoleptic patients.

The CHMP identified a concern for potential effects at sigma σ1 and σ2 receptors since the IC50 of pitolisant at these receptors (0.01 and 0.085 µM, respectively) is lower than the clinical Cmax at therapeutic doses of 20 mg (34.9 ng/mL or 0.118 µM) and 40 mg (72 ng/mL or 0.243 µM).

As pitolisant is a sigma-1 agonist, antidepressant activity and an abuse potential are theoretically plausible in humans. However, based on clinical data, a relationship between treatment with pitolisant and depressive symptoms cannot be excluded. Consequently, the risk of depression has been included as an important identified risk in the RMP and will be further characterized in the proposed PASS (see Clinical Safety).

Although pitolisant is sigma-2 antagonist and can theoretically attenuate some behavioural effects of cocaine, conflicting hypothesis regarding abuse potential could not lead to a definite conclusion. Therefore, abuse potential has been included in the RMP as important potential risk (see Clinical Safety).

In a mouse 4-week repeated dose toxicity study, conducted at doses of 30, 75 and 100 mg/kg/day the dose-level of 75 mg/kg/day of BF2.649 given by oral gavage to CB6F1-nonTgrasH2 mice was considered to be the NOAEL and elicited CNS signs of toxicity (mainly transient hypoactivity) in a limited number of mice. The incidence and severity of pale basophilic round bodies in the tubular lumen of the testes was increased at both 75 and 100 mg/kg/day. This finding was probably mouse-specific and did not appear to be associated with any other degenerative changes. The metabolite BP1.2526 was the major metabolite in both sexes over the study.

In the rat 13-week repeated dose toxicity study there was a lower heart weight. The aetiology of this finding and significance of the heart weight changes is not clear since they were stated not to be associated with any histopathological changes and no effect was found after the recovery period. At the top dose, which was reduced from 150 to 100 to finally 75 mg/kg/day, 30% of males and 20% of females were found dead as was one female (10%) in the recovery group. The cause of death is unknown, and necropsy did not reveal any apparent cause of death. The applicant speculated that the deaths could be due to a direct cardio-respiratory, or to a secondary CNS origin. The Applicant's conclusion that the cause of death in the rat has been identified as the convulsive activity of metabolites found in high concentrations in the rat (but humans) is not endorsed and is considered to be a hypothesis. However, in view of the fact that no signs of CNS toxicity similar to that observed in the rat have been reported in clinical studies or healthy volunteers at high doses provides some reassurance.

In the rat 6-month toxicity study the administration of 60 mg/kg/day for 6 months resulted in the death of several animals and was associated with severe overt signs of CNS toxicity such as convulsions, tremors and abnormal gait. The applicant proposed that the convulsive episodes could be linked to high $C_{max}$ values since they occurred close to the $T_{max}$. Focal increased alveolar macrophages (associated with pale foci at necropsy) were observed in 15/18 females at the top dose as compared to a limited number in other groups (4/20 in controls and 6/20 at 5 and 30 mg/kg/day). These changes were still present in the recovery 60 mg/kg/day females. However, males were almost not affected by these changes in lungs. In the 13-week rat study there were histopathological changes in lungs (pneumonia foci) in the top dose animals which were still present in the corresponding recovery animals. When these non-clinical findings are considered together with the clinical reports, it appears that there is no major pulmonary concern for the clinical use of pitolisant.

In the monkey 13-week study there appeared to be no treatment related effects at 5 mg/kg/day. At 12 mg/kg/day, occasional emesis and slight changes (within the normal range of values) in serum biochemistry were recorded in some animals and these effects stopped on treatment discontinuation. This dose was the NOAEL. In addition the main findings observed in several animals treated at 30 mg/kg/day were CNS signs (emesis, tremors), and slight changes in serum biochemistry. There was inter-day and inter individual variability in the toxicokinetics. Also drug exposure was not linear in the low part of the dose range. This could be related to a saturation of metabolic routes.

In the monkey 9-month study, central nervous system signs (tremors, unsteady gait and convulsions) were recorded at 30 mg/kg/day and the NOAEL dose was 12 mg/kg/day.

In regards to the CNS effects (convulsions), the applicant argued that a safety margin based on $C_{max}$ is more relevant than based on AUC leading to safety margins around 25, 10 and 1 for mice, rats and monkeys, respectively (convulsions occur at around the $T_{max}$). However, it would be more reliable to have a statistically significant correlation between convulsions and the $C_{max}$ taking into account high levels of pitolisant and overall metabolites in any species. Nevertheless, even based on $C_{max}$, the safety margin based upon the $C_{max}$ was still 1 for monkey.

Considering all of the toxicity studies overall, it is noteworthy that the adverse CNS effects occurred in all 3 animal species, in particular in the monkey. In the monkey the major *in vivo* metabolites are similar to humans qualitatively and quantitatively: the 2 major metabolites are the BP2.951 and the BP2.941. The metabolite BP1.2526 appeared to be more potent than pitolisant as pro-convulsive agent. Its serum and brain concentrations in rats are higher than those of pitolisant. However, this compound is present at very low levels in monkeys and therefore most probably only has a very limited role in CNS toxicity in this species. Therefore the entity responsible for the convulsions in monkey has not been clearly elucidated.

In general, low or no safety margins (based on AUC) were determined in toxicity studies. The main target organ was the CNS, with findings in line with safety pharmacology data showing that pitolisant induced a dose-dependent increase in central excitation leading to the appearance of convulsions.

Safety pharmacology studies highlighted the ability of pitolisant to affect the QT interval in humans (a thorough QT/QTc study was conducted further, see clinical section), as well as its pro-convulsant potential. The impact of this finding on the overall safety profile is discussed in the Clinical Safety section.

Pharmacodynamic drug interaction studies in rodents with drugs likely to be co-administered clinically, revealed no significant interactions.

Finally, there are no issues in relation to the impurity profile of the drug substance or drug product from a non-clinical perspective.

### 2.3.7. Conclusion on the non-clinical aspects

In conclusion the non-clinical data provided were considered sufficient to support this dossier.

## *2.4. Clinical aspects*

### 2.4.1. Introduction

The clinical development program of pitolisant included 34 clinical completed or ongoing phase 1 to 3 studies.

***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 6. Tabular listing of all clinical studies performed with pitolisant.**

| Type of study | Study number | Investigator | Objective of the study | Study design and type of control | Test product Dosage regimen Route of administration | Number of subjects* | Healthy subjects or Diagnosis of patients | Duration of treatment | Study status Type of report | Phase |
|---|---|---|---|---|---|---|---|---|---|---|
| BA/PK 5.3.1.2 | 03-01 | Guillaume M | Comparative BA of tablet versus capsule taken with and without grapefruit juice | Open, randomised, 2 way cross-over | Tablets 20mg and Capsules 20mg 20mg / dose x 3 periods Oral route | 8 (M) | Healthy volunteers | 1 single dose | Completed | I |
| PK/PD 5.3.3.1 | 02-02 | Guillaume M | PK/PD after 6 single ascending doses | Randomised Parallel, Double-blind placebo-controlled | Tablets 1 mg, 10 mg, 20mg 1mg or 5mg or 10mg or 20mg or 40mg or 60mg / dose Oral route | 36 (30) (M) | Healthy volunteers | 1 single dose | Completed | I |
| PK/PD 5.3.3.1 | 03-03 | Astruc B | Define PK, PD, tolerance of 2 multiple doses in young healthy volunteers +PD + satiety | Randomised parallel, double-blind, placebo-controlled | Tablets 20mg 40 mg / day Oral route | 8 (6) (M) | Healthy volunteers | Repeated doses 9 days | Completed | I |
| PK/PD 5.3.3.1 | 03-04 | Guillaume M | PK/PD after escalating doses of 90 and 120mg | Randomised parallel, double-blind, placebo-controlled. | Tablets 20 mg 90mg and 120mg /dose Oral route | 12 (10) (M) | Healthy volunteers | 1 single dose | Completed | I |
| PK/PD 5.3.3.1 | 04-06 | Guillaume M | PK repeated doses up to 28 days | Open-label | Tablets 20mg and 10 mg Doses: 40mg/ day for 14d and 50mg/day for 14d Oral route | 6 (M) | Healthy volunteers | Repeated doses 28 days | Completed | I |
| PK/PD 5.3.3.1 | 11-01 | Sidhu S | Mass balance study, metabolic profile | Open-label | $_{14}C$ 20mg capsules Dose : 20mg Oral route | 6 (M) | Healthy volunteers | 1 single dose | Completed | I |

| Type of study | Study number | Investigator | Objective of the study | Study design and type of control | Test product Dosage regimen Route of administration | Number of subjects* | Healthy subjects or Diagnosis of patients | Duration of treatment | Study status Type of report | Phase |
|---|---|---|---|---|---|---|---|---|---|---|
| PK/PD 5.3.3.1 | 03-08 | Hubert N | Interaction Olanzapine | Open -label | 20mg tablets Dose: 60mg Oral route | **6** (M) | Healthy volunteers | 1 single dose | Completed | I |
| PK/tolerability 5.3.3.2 | 11-11 | Lecendreux M | PK in patients from 6 to ≤18 years old | Open-label | 20 mg tablets Dose: 20mg Oral route | **24** planned (12M/12F) | Patients under 18yrs | 1 single dose | Study completed. CSR pending | I |
| PK/tolerability 5.3.3.2 | 07-02 | Arnulf I Möller C | Dose finding in Parkinson patients | Randomised, DB, placebo-controlled | 20 mg tablets Doses: 5mg, 10mg, 20mg, 40mg / day Oral route | 107 (**86**) (78M/29F) | Patients | Repeated doses 4 weeks | Completed | II |
| PK/tolerability 5.3.3.2 | 09-16 | Lévy P | Dose-finding study in moderate to severe OSA | Randomised, balanced, double-blind, parallel groups | Tablets 20mg Dose: 5mg, 10mg, 20mg, 40mg/ day Oral route | 116 (**91**) (95M/11F) | Patients | Repeated doses 14 days | Completed | II |
| QT 5.3.3.3 | 09-11 | Donazzolo Y | Effect of 2 doses (40 and 120 mg) on QTcF interval | Randomised, double-blind, 4 period, cross over, placebo-controlled | Tablets 20mg Doses: 40 mg and 120mg Oral route | **58** (25M/33F) | Healthy volunteers | 1 single dose | Completed | I |
| QT 5.3.3.3 | 14-05 | Latreille M | Effect of 3 doses (160, 200 and 240 mg) on QTcF interval | Randomised, double blind, single dose, placebo-controlled study | Tablets 20mg Doses: 160 mg, 200 mg and 240mg Oral route | **25** (25M) | Healthy male volunteers | 1 single dose | Completed | I |
| PK 5.3.3.3 | 09-12 | Donazzolo Y | Elderly patients | Open- label, Parallel group | Tablets 20mg One dose per day: 20mg Oral route | 25 (**12**) (12M/13F) | Healthy volunteers (≥68yrs) | Repeated doses 14 days | Completed | I |
| PK 5.3.3.3 | 09-13 | Donazzolo Y, Gatchev F | Renal impairment | Open- label, Parallel group | Tablets 20mg Dose: 20mg Oral route | **25** (21M/4F) | 12 HV/12 patients | 1 single dose | Completed | I |
| PK 5.3.3.3 | 09-14 | Donazzolo Y | Hepatic impairment | Open- label, Parallel group | Tablets 20mg Dose: 20mg Oral route | **24** (18M/6F) | 12 HV/12 patients | 1 single dose | Completed | I |

| Type of study | Study number | Investigator | Objective of the study | Study design and type of control | Test product Dosage regimen Route of administration | Number of subjects* | Healthy subjects or Diagnosis of patients | Duration of treatment | Study status Type of report | Phase |
|---|---|---|---|---|---|---|---|---|---|---|
| PK 5.3.3.4 | 11-03 Part I Part II Part III | Betting P | Relative bioavailability with itraconazole paroxetine; food interaction | Open, 2 way cross-over | Tablets 20mg 20mg / dose x 2 Oral route | 13/19/19 (M) | Healthy volunteers | 1 single dose | Completed | I |
| PK 5.3.3.4 | 11-10 | Betting P | Relative bioavailability with rifampicin | Cross-over, single sequence, two period, open label | 20mg tablets 1 dose: 20mg Oral route | 19 (M) | Healthy volunteers | 1 single dose at day 1 and at day 14 | Completed | I |
| Efficacy 5.3.5.1 | 05-03 | Bastuji H | Action on vigilance in narcoleptic patients | Single blind, Sequential placebo-controlled | 20mg tablets Dose: 40mg/day from Day 8 to Day 14 Oral route | 22 (14M/8F) | Patients | Repeated doses 14days | Completed | II |
| Efficacy 5.3.5.1 | 07-03 | Bassetti C | Effects in excessive daytime sleepiness (EDS) in narcoleptic patients with or without cataplexy: HARMONY 1 | Randomised, double-blind, placebo-controlled, Active-controlled, parallel group | Tablets 20mg Doses : 10 to 40mg l/day Oral route | 95 (31) (51M/44F) | Patients | Repeated doses 9 weeks | Completed | III |
| Efficacy 5.3.5.1 | 07-07 | Bassetti C | Efficacy on narcolepsy in a pitolisant versus pitolisant add on Modafinil study: HARMONY II | Randomised double-blind, parallel group | 20mg tablets Dose: 10mg or 20mg or 40mg per day Oral route | 14 (8M/6F) | Patients | Repeated doses 8 weeks | Completed | II |
| Efficacy 5.3.5.1 | 09-15 | Dauvilliers Y | Effects in excessive daytime sleepiness (EDS) in narcoleptic patients with or without cataplexy: HARMONY 1bis | Randomised, double-blind, placebo-controlled, Active-controlled, parallel group | Tablets 20mg Doses : 5 to 20 mg / day Oral route | 166 (67) (78M/88F) | Patients | Repeated doses 9 weeks | Completed | III |
| Efficacy 5.3.5.1 | 10-01 | Dauvilliers Y | Effects in EDS in narcoleptic patients on add on to oxybate: HARMONY IV | Randomised, double-blind, placebo-controlled, add on to oxybate | Tablets 20mg Dose: 10 to 40 mg per day Oral route | 48 (26) (34M/14F) | Patients | Repeated doses 8 weeks | Completed | III |

| Type of study | Study number | Investigator | Objective of the study | Study design and type of control | Test product Dosage regimen Route of administration | Number of subjects* | Healthy subjects or Diagnosis of patients | Duration of treatment | Study status Type of report | Phase |
|---|---|---|---|---|---|---|---|---|---|---|
| Efficacy 5.3.5.1 | 11-05 | Szakacs Z | Effect on weekly cataplexy attacks: HARMONY CTP | Randomised, double-blind, placebo-controlled, parallel group | Tablets 20mg Dose: 5 to 40 mg per day Oral route | **105 (54)** (53M/52F) | Patients | Repeated doses 8 weeks | Completed | III |
| Uncontrolled 5.3.5.2 | 06-06 | Bastuji H | Initial tolerability narcolepsy | Open label | 20mg tablets Doses:10mg, 20mg 40mg/ day Oral route | **26** (21M/5F) | Patients | 3 to 9 months | Completed | II |
| Uncontrolled 5.3.5.2 | 09-10 | Dauvilliers Y | Long term safety in narcoleptic patients: HARMONY III | Open-label | Tablets 20mg Dose: 5 to 40mg per day Oral route | **102** (45M/57F) | Patients | Repeated doses 1 year | Ongoing | III |
| Other 5.3.5.4 | 05-05 | Destée A | Efficacy pilot in Parkinson | Single-blind, placebo sequential-controlled | Tablets 20mg Dose: 40mg /day Oral route | **26** (20M/6F) | Patients | Repeated doses 7 days Open label 3 months | Completed | II |
| Other 5.3.5.4 | 06-10 | Arnulf I | Efficacy and safety in Parkinson patients HARPS 1 | Randomised, double-blind, placebo-controlled, parallel group | Tablets 20mg Dose: 5mg, 10mg, 20mg /day Oral route | 235 (221)* (179M/56F)[b] | Patients | Repeated doses 12 weeks Ext 9 months | Completed | III |
| Other 5.3.5.4 | 06-11 | Eggert K.M. | Efficacy and safety in Parkinson patients HARPS 2 | Randomised, double-blind, placebo-controlled, parallel group | Tablets 20mg Dose: 5mg, 10mg, 20mg /day Oral route | 231 (202)* (160M/71F)[b] | Patients | Repeated doses 12 wk Ext 9 months | Completed | III |
| Other 5.3.5.4 | 04-01 | Levy P | Efficacy pilot in Obstructive Sleep Apnea OSA, effect of placebo | Single blind, Placebo-sequential controlled, | 20 mg tablets Dose: 40mg at day 3, 4, 5; placebo at day 1, 2 and 6, 7 Oral route | **12** (M) | Patients | Repeated doses 7 days | Completed | II |
| Other 5.3.5.4 | 05-01 | Pepin JL | Exploratory study OSA | Single-blind, placebo sequential-controlled | Tablets 20mg Dose: 40mg/ day Oral route | **21** (M) | Patients | Repeated doses 14 days | Completed | II |

| Type of study | Study number | Investigator | Objective of the study | Study design and type of control | Test product Dosage regimen Route of administration | Number of subjects* | Healthy subjects or Diagnosis of patients | Duration of treatment | Study status Type of report | Phase |
|---|---|---|---|---|---|---|---|---|---|---|
| Other 5.3.5.4 | 04-07 | Hirsch E | Safety and effect in refractory partial seizures | Open | Tablets 20mg Dose: 20 to 40mg /day Oral route | **23** (13M/10F) | Patients | Repeated doses 3 months | Completed | II |
| Other 5.3.5.4 | 05-08 | Pasquier F | Efficacy and tolerance in Lewy's body dementia | Randomised, double-blind, placebo controlled, parallel group Extension phase | Tablets 20mg Doses: 10mg, 20mg, 40mg /day Oral route | 36 (**19**) | Patients | Repeated doses 3 months Extension: 39 weeks | Completed | II |
| Other 5.3.5.4 | 05-07 | Mendlewicz J | Efficacy and tolerance in ADHD | Single -blind | Tablets 20mg Doses: 10mg, 20mg, 40mg /day Oral route | 35(**32**) (17F/18M) | Patients | Repeated doses 4 weeks Extension 8 weeks | Completed | II |
| Other 5.3.5.4 | 04-08 | Bourin M | Efficacy and tolerance in Schizophrenia in addition to olanzapine | Randomised, double-blind, placebo controlled | Tablets 20mg Doses: 40mg /day Oral route | 12 (**6**) (6F/6M) | Patients | Repeated doses 3 months | Abridged | II |
| Other 5.3.5.4 | 03-06 | Hirsch E | Action on photosensitivity in epileptic patients | Single blind | 20mg and 10mg tablets Dose: 20mg, 40mg, 60mg Oral route | **14** (12F/2M) | Epileptic patients | 1 single dose | Completed | II |

* Number of randomized subjects (with number of subjects taking pitolisant in bold) (gender)

[a] P06-10: 221 patients exposed: 151 exposed to BF2.649 in double-blind phase (period 1) plus 70 from placebo arm who continued open label extension phase (period 2);
P06-11: 202 patients exposed: 159 exposed to BF2.649 in double-blind phase (period 1) plus 43 from placebo arm who continued open label extension phase (period 2).

[b] P06-10: gender 235 (179M/56F) for double blind phase, safety population;
P06-11: gender 231 (160M/71F) for double blind phase, safety population.

## 2.4.2. Pharmacokinetics

***Absorption***

Following single and multiple oral dosing of pitolisant to healthy male adults at doses between 1 and 240 mg, absorption was reasonably rapid with $C_{max}$ typically achieved between 2 and 4 hours after dosing. Exposure to pitolisant showed moderate to high interindividual variability and increased more than proportionally with dose up to 240 mg after once daily dosing. In the therapeutic dose range, $AUC_{0-\infty}$ increased by about 2.3 when pitolisant dose is doubled from 30 to 60 mg.

According to a mass-balance study conducted in 6 healthy male subjects dosed with 20 mg in fasting state, a mean recovery of at least 88% of administered radioactivity was recovered, primarily from urine (approximately 63%) with approximately 25% of the dose excreted through expired air and a small fraction (<3%) recovered in faeces. The absolute bioavailability of pitolisant has not been determined.

The food intake significantly decreases the systemic exposure of pitolisant (significant decrease in $C_{max}$ and AUC). A delay of absorption was observed (significant increase in $T_{max}$ with food intake). Nevertheless, the extent of absorption (AUC) remains bioequivalent with or without food.

Basing on the results above, it can be considered that there is a potential effect of food intake on the bioavailability, specifically on the rate of absorption, of pitolisant. However, no clinical consequences are expected. The SmPC of pitolisant recommends taking pitolisant during breakfast for tolerability and not PK reasons. This recommendation was endorsed by the CHMP.

Based on PK parameters estimated using NCA approach, pitolisant PK parameters exhibit a moderate to high between-subjects variability. Within-subjects variability (%CV) could not be estimated from the available data.

***Distribution***

Pitolisant was moderately bound to serum proteins at therapeutic concentrations (~78-96%). The parent drug has a high apparent volume of distribution (V/F; 1100 to 2825 L). However, there was no reliable estimation of pitolisant apparent Vd due to discrepancies between studies. This seems to be linked to the high intersubject variability and to the nonlinear PK of pitolisant (mainly time-dependency). As the bioavailability of the drug is unknown, it was not possible to say whether the high apparent volume of distribution is due to large extent of distribution or low bioavailability. *In vitro* investigations showed that pitolisant distributes to red blood cells (RBC) with equal affinity to that of plasma proteins. Pitolisant crosses the blood-barrier barrier in animal models.

The half-life of pitolisant was estimated to be between 8-11 hours (median values).

***Elimination***

The main route of elimination of pitolisant is hepatic metabolism. The mass balance study showed that excretion (renal or biliary) does not play an important part in the elimination of parent drug. The metabolites were excreted in urine and presumably expired air (as $CO_2$). It is claimed that approximately 25% of administered radioactivity could be accounted for in expired air, however the methods, assumptions and impact on study conclusions were not detailed and therefore could not be endorsed by the CHMP. The Applicant committed to perform a new mass-balance study with the drug radiolabelled at a non-labile position.

A human metabolic pathway for pitolisant based on the *in vivo* and *in vitro* investigations was submitted to the authorities.

***Pharmacokinetics in target population***

No investigation on pitolisant PK has been made on the target population. No marked differences are expected in target patients compared to healthy volunteers.

***Dose proportionality and time dependencies***

Analysis of the available data indicates that pitolisant PKs is not linear. The drug exposure appeared to be greater than proportional to dose and may also be time-dependent. After repeated dose administration, the drug accumulated more than expected from single dose studies.

***Special populations***

In both renal and hepatic impairment, drug exposure increased. After single dose administration, in mild, moderate and severe renal impairment, total drug exposure increased approximately 2-fold. In moderate hepatic impairment, unbound drug exposure increased by 3.3-fold.

Most studies were performed in healthy male subjects. Therefore, no conclusion could be made regarding the influence of gender on pitolisant pharmacokinetics.

All pharmacokinetic studies were conducted in European countries and the potential effect of ethnicity on pitolisant pharmacokinetics has not been investigated. There was also no investigation on the influence of body weight or body surface area.

Study P09-12 conducted to assess the pharmacokinetic profile in healthy elderly subjects and a young adult control group showed that pitolisant exposure was higher in the elderly whilst apparent clearance was lower. Moreover, a high variability and therefore important fluctuation were observed.

***Pharmacokinetic interaction studies***

*In vivo* PK interactions studies were conducted by the Applicant to assess the clinical impact of the combination of pitolisant with potent CYP3A4 and 2D6 inhibitors or inducers.

The co-administration of multiple doses of itraconazole (200 mg for 7 days), a potent CYP3A4 inhibitor, with pitolisant (single dose of 20 mg) in 18 healthy subjects had no significant impact on rate of absorption and extent of exposure of the parent drug. It induced a slight decrease of exposure to the metabolite BP2.951 (14 and 11% for $AUC_{0-t}$ and $AUC_{0-\infty}$ geometric means, respectively). $C_{max}$ for the metabolite was decreased (about 27%). $T_{max}$ was not modified.

The co-administration of multiple doses of rifampicin (600 mg for 7 days), a potent CYP3A4 inducer, with pitolisant in 18 healthy male subjects significantly decreases extent of exposure of pitolisant (39%, 47% and 48% for $C_{max}$, $AUC_{0-t}$ and $AUC_{0-\infty}$ geometric means, respectively); the 90% CIs being excluded from the reference range [0.80-1.25]. It did not modify BP2.951 $C_{max}$ and decreases exposure to BP2.951 (38% and 37% for $AUC_{0-t}$ and $AUC_{0-\infty}$ geometric means, respectively). Given the approximately 50% decrease of pitolisant exposure with rifampicin, it can be concluded that co-administration of pitolisant with inducers of CYP3A4 should be done with caution.

The co-administration of multiple doses of paroxetine (20 mg for 8 days and 10 mg for 1 day), a potent CYP2D6 inhibitor, with pitolisant (20 mg, single dose) in 18 healthy subjects significantly increases the rate of absorption and extent of exposure of pitolisant (47%, 105% and 121% for $C_{max}$, $AUC_{0-t}$ and $AUC_{0-\infty}$ geometric means, respectively). It resulted also in a slight decrease of $C_{max}$ of the metabolite (about 4.6%) and in a significant increase of exposure to BP2.951 (63% and 84% for $AUC_{0-t}$ and $AUC_{0-\infty}$ geometric means, respectively).

*In vitro* data showed inhibition of CYP2D6 by pitolisant but at concentrations higher than the worst calculated cases. Nonetheless, a study performed in mice showed a 2.3-fold increase of olanzapine exposure in serum and a 3.2-fold increase in the brain after a co-administration with pitolisant (n=9). Then, according to these results, a clinical study was planned to see if such effect may occur in human.

Surprisingly, when olanzapine 5 mg was co-administered with pitolisant 60mg in 6 healthy subjects, a significant decrease of olanzapine plasma concentrations (around 20%) was observed with a significant increase of pitolisant plasma concentrations (around 20%, with 90% confidence interval outside the bioequivalence bounds of [0,8-1,25]).

On the contrary, the exposure of olanzapine 2.5 mg was a little higher than with 5mg (i.e. ratio for the AUC 1.38 versus 1.18). These results support the previous assumption that interaction data in animals cannot be extrapolated to human.

***Pharmacokinetics using human biomaterials***

CYP450 isoenzymes study set up was generally appropriate with adequate cell models (human liver microsomes or primary culture of human hepatocytes) and control substrates for each studied cytochrome (CYP1A2, CYP2C9, CYP2D6 and CYP3A).

Studies assessing the inhibitory potential of pitolisant were performed with acceptable range of pitolisant concentrations (0 up to 25 µM) covering the worst systemic concentrations of 50 × Cmax,u, i.e. 1.25 µM. Nonetheless, for CYP3A4, the tested concentrations would have considered the worst intestinal one (i.e. 0.1 × D/250 ml or 54 µM) since this isoenzyme is also located in enterocytes.

Results showed a moderate inhibitory potential of pitolisant, IC50s being >100 and 2.6 µM with CYP3A4 and CYP2D6 isoforms, respectively. These values are notably higher than the estimated cut-off values, i.e. 1.25 µm and 54 µM at the systemic and the intestinal level, respectively, suggesting that pitolisant is not expected to modify the metabolism of drugs substrates of these isoenzymes. In this respect, it should be underlined that inhibition of CYP2D6 by pitolisant was not a mechanism-based inhibition. In agreement with the *in vitro* data, degradation of drugs like midazolam, phenacetin, diclofenac and S-mephenytoin by human microsomes was not modified in presence of pitolisant. Then, clinically relevant interactions related to CYP3A4, 1A2, 2C9 and 2C19 inhibition by pitolisant is unlikely.

*In vitro* studies show no ability for pitolisant and of its three major metabolites in human to be UGT inhibitors or inducers.

Pitolisant has been shown to have high permeability in Caco-2 cells assay. It is neither a P-gp nor a BCRP substrate, each efflux ratio (ER) < 2. Therefore, no drug-drug interactions related to an inhibition or induction of these transporters are expected.

With regards to P-gp and BCRP inhibition, pitolisant displayed an IC50>270 µM for both efflux transporters. With cut-off values at the intestinal and systemic level of 1.25 µM ($50 \times C_{max,u}$ for the highest therapeutic dose = 40 mg/day) and 54µM (0.1× D/250mL), respectively, the IC50 is higher than theses values. Therefore, clinically relevant interactions due to P-gp and BCRP inhibition by pitolisant are unlikely.

Additional *in vitro* studies were performed to investigate the ability of pitolisant to be a substrate of the uptake transporters OATP1B1, OATP1B3, OCT1, OCT2, OAT1, OAT3, and efflux transporters MATE-1 and MATE-2K. Based on the provided results, the following conclusions and *in vitro-in vivo* extrapolation were made according to the EU Guideline of Drug Interaction Investigations:

- Pitolisant is neither an OATP1B1, OATP1B3 nor an OCT1 substrate. Therefore, no drug-drug interactions related to an inhibition these transporters are expected.

- Pitolisant does not inhibit MATE-1, MATE-2K, OAT1, OAT3 and OCT2 at a concentration higher than the worst expected concentration at the systemic level, i.e.50× $C_{max,u}$ ~1,~25 µM. Therefore no interaction related to inhibition of these transporters by pitolisant is expected at the therapeutic concentrations.

- Pitolisant inhibits OATP1B1 and 1B3 with an IC50> 322 µM and 181 µM, respectively. According to the estimated cut-off value at the hepatocyte level, for both uptake transporters, of 21.5 µM (25×$C_{inletu}$ for the highest therapeutic dose = 40 mg/day), these IC50 are far higher. Therefore, a clinically relevant interaction due to OATP1B1 and OATP1B3 inhibition by pitolisant is unlikely.

- Pitolisant inhibits OCT1, with an IC50<1.33 µM (the lowest concentration tested) which is close to the estimated cut-off value at the hepatocyte level, for this transporter, of 21.5 µM (25×$C_{inlet\ u}$ for the highest therapeutic dose = 40 mg/day).

## 2.4.3. Pharmacodynamics

***Mechanism of action***

Pitolisant is an active antagonist/inverse agonist (Ki of 0.3 nM) of the human histamine H3 receptor (H3R). It triggers a long-lasting activation of histaminergic neurons in brain, a neuronal system involved in the maintenance of wakefulness, attention and cognition. Pitolisant crosses the blood-brain barrier and elicits histamine release in the whole CNS accompanied by release of other wake-promoting neurotransmitters (dopamine, noradrenaline and acetylcholine) in cerebral cortex, presumably via an indirect mechanism. Dopamine release in nucleus accumbens is not affected, which differentiates it from other wake-promoting agents i.e. amphetamine-like psychostimulants.

***Primary pharmacology***

Studies in healthy volunteers after single and repeated doses of pitolisant have included various psychometric tests as well as quantitative EEG recording to investigate the effects of Pitolisant on vigilance, attention, coordination, memory, sleep and satiety.

In study P02-02 (double-blind, randomized, placebo-controlled single dose study), 36 healthy volunteers received single oral dose of pitolisant (1, 5, 10, 20, 40 or 60 mg) or placebo. Results from qEEG showed that activities increased two hours after single 40 and 60 mg of pitolisant oral administration on anterior leads (20-30 Hz band) and posterior leads (16 to 40 Hz bands).

In study P03-03 (double-blind, ascending, placebo-controlled, multiple dose study), 8 healthy volunteers received repeated oral dose of pitolisant 40 mg/d (n=6) or placebo (n=2) for 9 days. Results from qEEG records indicate that pitolisant is associated with a trend of increasing beta frequencies in the anterior leads, and decreasing the alpha frequencies more markedly in the posterior leads.

***Secondary pharmacology***

A dedicated QT study (a randomised, double-blind, 4-periods, crossover study), comparing single doses of 40 mg and 120 mg of pitolisant to a single dose of 400 mg of moxifloxacin and to placebo was conducted to assess the effect of pitolisant on ventricular repolarization. This study showed that pitolisant at 40 mg/d did not increase the QTc (mean observed variation of 3.7 ms; with 5.9 ms for upper bound of the CI90%). However, at the supra-therapeutic dose of 120 mg/d, the mean change was ~10 ms, with an upper bound of the CI 90% of 12.2 ms, suggesting a risk of QT/QTc prolongation at this dose of 120 mg.

Effects of pitolisant on QTcF interval at supra-therapeutic doses are confirmed by results from the additional Phase I study, where following pitolisant doses of 160 mg, 200 mg and 240 mg, the ΔΔQTcF was >5 ms at the three 3 doses, with a 95% upper bound of the predicted effect above 10 ms (11.9, 13.3 and 9.9 ms respectively).

***Pharmacodynamic interactions with other medicinal products or substances***

Concomitant administration of tri or tetracyclic antidepressants (e.g. imipramine, clomipramine, mirtazapine) and anti-histamines (H1-receptor antagonists) crossing the hemato-encephalic barrier (e.g. pheniramine maleate, chlorpheniramine, diphenydramine, promethazine, mepyramine) with pitolisant is not recommended since the endogenous histamine released in brain by these treatments could be altered.

No clinical data supporting this assumption were provided. However, this interaction is pharmacologically plausible since pitolisant and these two classes of products target the same histamine brain receptors.

## 2.4.4. Discussion on clinical pharmacology

In addition to nonclinical pharmacokinetic studies (*in vitro* metabolite profiling, CYP inhibition and induction, P-gp substrate evaluation and protein binding), clinical pharmacology investigation has been performed in humans. Full PK profiling has been performed in a total of 14 PK studies. A population PK analysis of pooled data of healthy subjects (male and female, young and elderly) has been submitted and showed that i) pitolisant could be modelled according to a bi-compartmental model with a 0-order absorption, ii) pitolisant $t_{1/2}$ was within a range centered on 10-11 h. This means that, considering a once daily administration, steady-state should be reached within less than one week; and iii) CL/F was found to decrease with both pitolisant dose and duration of administration

The primary pharmacology data were obtained from qEEG recording in healthy volunteers. Even though limited, these data suggest an effect of pitolisant on vigilance and arousal.

Several analytical methods by liquid chromatography were developed to measure pitolisant and/or its metabolites. All methods employed in the PK studies (except those used in the mass-balance study) have been validated and their performances were fit for purpose.

The CHMP identified several shortcomings in the documentation provided on the pharmacokinetics of pitolisant. There were many discrepancies between the values of PK parameters in the different studies reports. Despite further analysis of the available data provided by the Applicant, there still are gaps in the understanding of the pharmacokinetics of the drug, introducing uncertainty in the assessment of the safety and efficacy of the product when administered to different subgroups or when co-administered with other drugs. These gaps include basic pharmacokinetic properties of pitolisant. Major elimination pathways are insufficiently understood for the drug and require additional investigations. Therefore, the Applicant has been requested to perform a new balance study after repeated dose administration in order to identify the major metabolites and characterize their PK behaviour and the mechanisms underlying their formation. This study will be conducted as a post-approval measure.

Considering the non-linearity of pitolisant and the pronounced time-dependency, the PK of the drug in patients with renal and hepatic impairment could not be safely predicted from the single-dose study data, especially as the mechanism underlying this non linearity is still unknown. Therefore, the SPC has been amended in order to reflect the lack of data in these sub-groups of patients. Influence of severe hepatic impairment (Child-Pugh C) on pitolisant PK was not investigated. Consequently, a corresponding contraindication has been introduced in the SmPC.

Understanding of the pharmacokinetics of pitolisant in the elderly was considered insufficient, particularly noting the doubling of drug exposure noted in renal impairment patients (mild to severe). Very limited data are available in this sub-group of patients precluding safe recommendations. This lack of information has been reflected in the SPC.

PK investigations have been carried out on the three major metabolites in humans BP2.951, BP1.8054 and BP1.9733. Based on calculated IC50, the major metabolite BP2.951 showed a weak inhibitory potential on CYP2D6 and 2C19 but this is not expected to have any clinically relevant impact at the circulating concentrations. The two other major metabolites are devoid of inhibitory potential on major CYP and UGT isoforms.

*In vitro* studies have shown the inducing effect of pitolisant as well as of BP2.951 and BP1.8054, two of the three main metabolites, on CYP1A2, CYP3A4 and CYP2B6. Only with CYP3A4 and CYP2B6, this effect is expected to be clinically relevant. Therefore, the CHMP requested that the impact of pitolisant on CYP3A4 and CYP2B6 will be investigated in a DDI study with probe CYP3A4 and CYP2B6 substrates post-approval.

The CHMP also requested that the Applicants conducts post-approval study assessing pitolisant pharmacokinetics in CYP2D6 poor metabolizers. This issue has been considered to be an important safety risk knowing the major involvement of CYP2D6 in the overall metabolic clearance of pitolisant.

Based on the results of itraconazole study, the CHMP concluded that clinically relevant interactions following the co-administration of pitolisant with inhibitors of CYP3A4 is unlikely. However, these results were not expected since in vitro data demonstrated the major role of CYP3A4 (and CYP2D6) in the metabolism of pitolisant, in accordance to the significant decrease (about 50%) of pitolisant exposure observed with rifampicin.

The results of paroxetine study were consistent with *in vitro* data that showed the involvement of CYP2D6 in the metabolism pathway of pitolisant. Given the 2-fold increase of pitolisant exposure when co-administered with paroxetine and the safety profile of pitolisant from phase II and III trials, the CHMP concluded that co-administration of pitolisant with inhibitors of CYP2D6 (including some antidepressants) should be done with caution and appropriate warning was included in the SmPC.

The mechanism explaining results of olanzapine study is unclear. The Applicant proposed a possible competition between olanzapine and pitolisant 60mg on the intestinal sites of the P-gp efflux proteins. Olanzapine would have a higher affinity for this protein, leading to an increase of pitolisant exposure. However, the current non clinical data show that pitolisant is not P-gp substrate. Additionally, as regard to olanzapine, a CYP2D6 inhibition by pitolisant cannot be supported because olanzapine is mainly metabolized by UGT1A4 and CYP1A2.

Furthermore, even though DDI studies are not sufficiently powered to assess the safety profile of a combination, this study did not indicate any clinically meaningful trend. Indeed, the co-administration of pitolisant 60 mg with olanzapine 5 mg appeared to reduce the deleterious effects of olanzapine on vigilance and satiety, while maintaining a good tolerance. No clear correlation between the pitolisant and olanzapine co-administration dose level could be established when investigating the pharmacodynamic and pharmacokinetic profiles.

The pharmacokinetic interactions of pitolisant on olanzapine, and vice versa, were statistically significant but the low number of subjects included, the conflicting results with both olanzapine doses 2.5 and 5 mg, compared to in vitro and theoretical data, do not allow a conclusion to be drawn. Based on in vitro data, the CHMP agreed that pitolisant and its main metabolites are not expected to inhibit CYP2D6 in a clinically relevant way.

No data have been submitted around potential interactions related to UDP-glucuronosyltransferase (UGT) in the original application. However, several glucuronide and sulphate conjugated metabolites were identified in humans with two major ones (greater than 10%) corresponding to a glycine conjugate and a glucuronide metabolite of pitolisant. Furthermore, considering pitolisant as a victim drug, clinical data related to CYP3A4 appeared inconsistent compared to *in vitro* data. The co-administration of rifampicin, a potent CYP3A4 inducer, with pitolisant decreased the extent of exposure of pitolisant by about 50%, while itraconazole, a potent CYP3A4 inhibitor, did not significantly affect PK of pitolisant. As rifampicin also induces 2C8/2C9, not originally identified as contributing to the elimination of pitolisant, these results raised a concern on the possible involvement of other enzymes in the metabolism of pitolisant such as UGTs (rifampicin acts also as an inducer of UGTs). Consequently, the lack of any data from *in vitro* interaction studies with UGTs has been identified as an important gap. The *in vitro* study submitted in response to this concern showed no ability for pitolisant and of its three major metabolites to be an UGT inhibitor. The Applicant has also submitted *in vitro* study data showing that pitolisant and its three major metabolites are devoid of induction potential of UGT isoforms.

As pitolisant undergoes glucuronidation mainly by UGT 2B7, the CHMP was of the opinion that impact of an inhibitor on this enzyme should be assessed. Consequently, a DDI study investigating this issue has been included in the RMP as post-approval measure.

The genetic polymorphism of the iso-enzyme CYP2D6 and UDP-glucuronosyltransferase is known to modulate the enzyme capability. The CHMP noted that in a number of pharmacokinetic studies samples were collected to determine 2D6, 3A4 and PgP genotype. CYP2D6 seems to be involved in pitolisant metabolism so in order to evaluate the impact of CYP2D6 polymorphism, 3 PMs will be investigated in the above mentioned new mass-balance study.

Pitolisant may be administered with modafinil or oxybate. It is expected that modafinil, as a moderate enzyme inducer, would give rise to decrease pitolisant exposure. Therefore, the interaction potential between these drugs will be investigated in a currently ongoing clinical interaction study. This study has been included as post-authorisation measure in the RMP.

### 2.4.5. Conclusions on clinical pharmacology

The CHMP considers the following measures necessary to address the issues related to pharmacology:

The Applicant should perform the following studies:

- A mass balance study with drug radiolabelled in a non-labile position. This ADME investigation should be performed at steady state.

- A study assessing pitolisant pharmacokinetics in CYP2D6 poor metabolizers.

- DDI study with CYP3A4 and CYP2B6 probe substrates.

- DDI study with an UGT2B7 inhibitor. In case of inconclusive results, the Applicant will have to further investigate the elimination profile of pitolisant.

- DDI studies with modafinil and sodium oxybate.

## *2.5. Clinical efficacy*

In the treatment of excessive daytime sleepiness (EDS), pitolisant was tested in Obstructive Sleep Apnoea (OSA) disease, Parkinson disease and narcolepsy.

Four phase II studies were conducted in Parkinson disease (P05-05, P06-10, P06-11 and P07-02) and three in OSA (P04-01, P05-01 and P09-16).

Narcolepsy development program included 8 phase II/III open-label, simple or double-blind studies (see Table 7 below), of which two (P07-03 [Harmony I] and P09-15 [Harmony Ibis]) were considered pivotal for the claimed indication in the treatment of narcolepsy with or without cataplexy in adults.

**Table 7. Pitolisant clinical studies in narcolepsy.**

| Study | Objective of the study | Study design | Dosage regimen | Number of subj. | Duration of treat. | Study status | Phase |
|---|---|---|---|---|---|---|---|
| 05-03 | Action on vigilance in narcoleptic patients | Single blind, Sequential placebo-controlled | 20mg tablets Dose: 40mg/day from Day 8 to Day 14 | 22 (14M/8F) | Repeated doses 14days | Completed | II |
| 06-06 | Initial tolerability narcolepsy | Open label | 20mg tablets Doses:10mg, 20mg, 40mg per day | 26 (21M/5F) | 3 to 9 months | Completed | II |
| 07-03 | Effects on EDS in narcoleptic patients with or without cataplexy: HARMONY I | Randomized, double-blind, placebo- controlled, Active-controlled, parallel group | Tablets 20mg Doses : 10 to 40mg per day | 95 (31) (51M/44F) | Repeated doses 9 weeks | Completed | III |
| 07-07 | Efficacy on narcolepsy in a pitolisant versus pitolisant add on Modafinil: HARMONY II | Randomized double-blind, parallel group | 20mg tablets Dose: 10mg or 20mg or 40mg per day | 14 (8M/6F) | Repeated doses 8 weeks | Completed (interrupted) | II |
| 09-15 | Effects on EDS in narcoleptic patients with or without cataplexy: HARMONY Ibis | Randomized, double-blind, placebo- controlled, Active-controlled, parallel group | Tablets 20mg Dose: 5 to 20 mg per day | 166 (67) (78M/88F) | Repeated doses 9 weeks | Completed | III |
| 09-10 | Long term safety in narcoleptic patients: HARMONY III | Open-label | Tablets 20mg Dose: 5 to 40mg per day | 102 (45M/57F) | Repeated doses 1 year | Ongoing | III |
| 10-01 | Effects on EDS in narcoleptic patients in add-on to oxybate: HARMONY IV | Randomized, double-blind, placebo- controlled, add on to oxybate | Tablets 20mg Dose: 10 to 40 mg per day | 48 (26) (34M/14F) | Repeated doses 8 weeks | Completed | III |
| 11-05 | Effect on weekly cataplexy rate: HARMONY CTP | Randomized, double-blind, placebo- controlled, parallel group | Tablets 20mg Dose: 5 to 40 mg per day | 105 (54) (53M/52F) | Repeated doses 8 weeks | Completed | III |

## 2.5.1. Dose response studies

No formal dose-finding study in narcolepsy was performed which was justified by the Applicant by the difficulties to recruit patients in this orphan indication.

The data available from two phase II studies (P05-03 and P06-06) in narcoleptic patients support the use of pitolisant in a titration scheme, i.e. instauration at a progressive increase-dose until the normalisation of symptomatology and as far as no adverse event occurs; and in case of signs of over-dosage, reduction of the dose to the immediate lower level.

In P05-03 study, a sequential 2-week single arm, single-blind, phase II trial, pitolisant was given at an oral dose of 40 mg for one week (after one week of placebo) in 22 narcoleptic patients. In this study, pitolisant reduced the excessive diurnal somnolence with an improvement of the ESS score of 4.89 ± 1.32 compared to placebo period (p=0.0006). The reported adverse events in this study were more frequently observed during the 3 first days of treatment supporting a titration therapeutic scheme, starting with a lower dose than 40 mg/day.

P06-06 study was a multicentre, open-label, uncontrolled phase II study. In this study, pitolisant was given in an escalating dose regimen (10, 20 or 40 mg/day) for up to 9 months in 26 narcoleptic patients. Pitolisant was started at the dose of 10 mg/day during the first week and this dose was continued or increased up to 40 mg/d during the next three weeks according to the opinion of the investigator on the basis of the efficacy and the tolerance. Pitolisant reduced the mean ESS scores by 4.8, 5.3 points and 6.9 points after 1, 3 and 9 months of treatment, respectively.

In addition, the Applicant provided results from two dose-finding studies conducted in EDS in Parkinson disease (P07-02) and obstructive sleep apnoea (OSA) (P09-16) to justify the dose selection.

Study P07-02 was a double-blind parallel group trial comparing placebo to four daily doses of pitolisant (5, 10, 20 and 40 mg) in the treatment of EDS in Parkinson disease patients. The primary endpoint was ESS scores change between the treatments groups, on the 4-week treatment period. In the IT population, the ESS score change between inclusion and final visits (primary endpoint) did not show significant difference between the 5 treatment groups (p=0.069). However, it was concluded that on an IT basis, using Linear Contrasts (analysis used for the assessment of a monotonic increase of measured endpoints with different doses), a significant increasing effect of dose on efficacy was found (p=0.0176) with pitolisant on ESS: the higher was the dose, the better was the efficacy, and by using step-down contrasts, the 20 mg dosage was identified as the MED (minimum effective dose), p=0.0357.

Study P09-16 was a double-blind parallel group trial comparing placebo to four daily doses of pitolisant (5, 10, 20 and 40 mg) in the treatment of EDS in obstructive sleep apnoea syndrome. The primary endpoint was ESS scores change between the treatments groups over 2 weeks. The results from this study showed that pitolisant decreased daytime sleepiness in a dose-dependent manner (p=0.0003). ESS reduction between baseline and final visit was: -4 for 5 mg/d group, -4.7 for 10 mg/d group, -7 for 20 mg/d, and -8.2 for 40 mg/d in patients with nCPAP (Continuous Positive Airway Pressure). Similar results were observed in patients refusing nCPAP and overall population.

Since narcolepsy, Parkinson and OSA are different diseases, the “extrapolation” of results from the two later studies should be used with caution. Study P09-16 was conducted after the completion of the first pivotal study (Harmony I), but before the second pivotal study (Harmony Ibis).

Results from study P04-06 (PK study conducted in 6 healthy volunteers receiving a repeated oral dose of 40 mg of pitolisant for 14 days, and according to the tolerability, were to receive a repeated oral dose of 50 mg or 30 mg for other 14 days) showed that the repeated dose of 50 mg/d of pitolisant during 14 days after other 14 days at 40 mg/d was well-tolerated.

The justification for not using the upper dose (40 mg/d) in the second pivotal study was related to the results from the first pivotal study (Harmony I) showing that 12 out of 32 (37.5%) patients from pitolisant arm stayed at this dose until the end of the study. Moreover, the 20 mg/d group showed numerically better results on ESS scores (mean final score=8.1; reduction of 9.1 points from baseline) than 40 mg/d group (mean final score=12.9; reduction of 5.3 points from baseline) (see results of Harmony I and Ibis in the respective sections).

## 2.5.2. Main studies

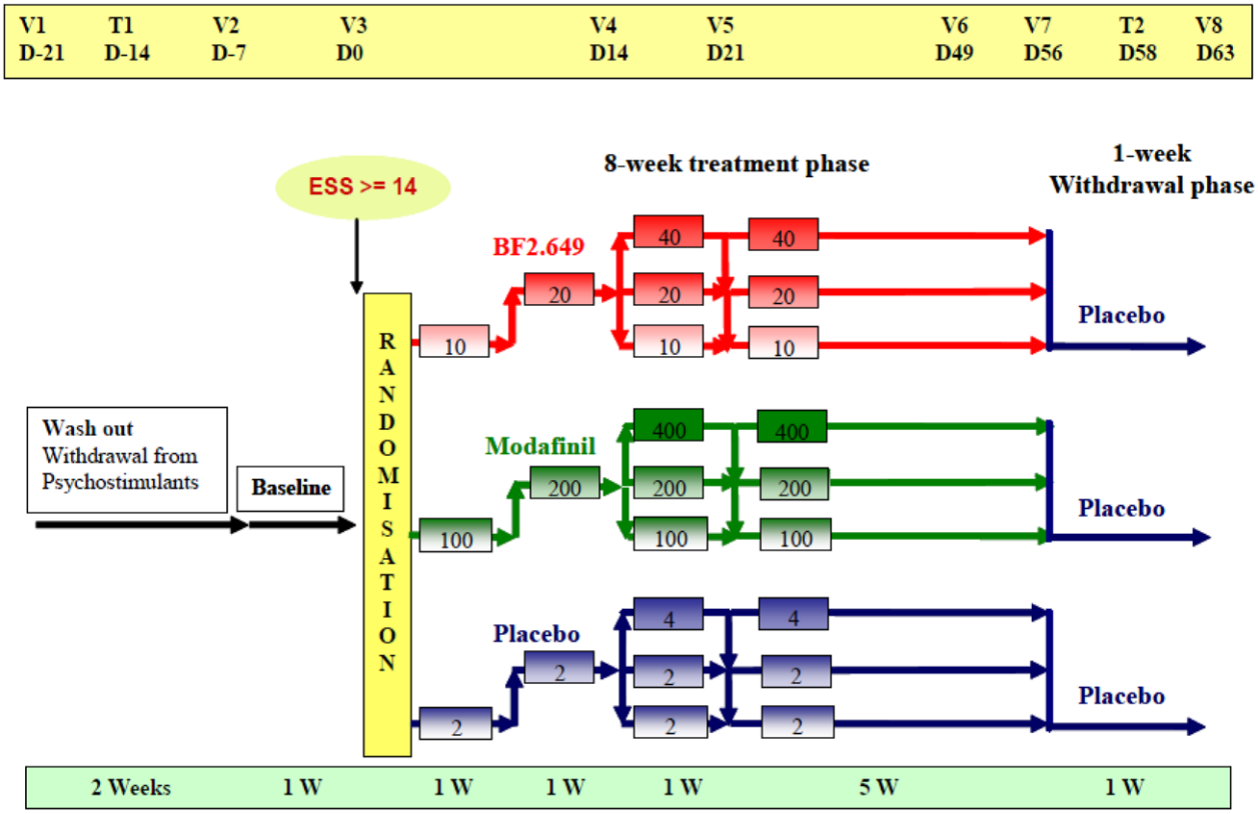
**Study 07-03 Prospective, randomized double-blind study, placebo-controlled, parallel-group, multi-center trial assessing the effects of BF2.649 in treatment of excessive daytime sleepiness in narcolepsy (Harmony I)**

***Methods***

**Study design**

The schematic representation of study design is presented in Figure 1 below.

**Figure 1. Study P07-03 (Harmony I) design.**




***Study Participants***

Adult male and female subjects in good physical health who met the International Classification of Sleep Disorders (ICSD-2) criteria for narcolepsy with or without cataplexy were eligible for inclusion in this study. The required EDS score was ≥ 14 points/24 at baseline.

Patients had to be free of drugs or discontinue any psychostimulant medications for at least 14 days at the start of baseline period. Patients with severe cataplexy were permitted to remain on stable dose of their anticataplectic (oxybate) or supposed anticataplectic medications (antidepressant or SSRIs).

***Treatments***

Pitolisant, modafinil and placebo were provided as capsules. Each capsule contained either tablets (pitolisant or modafinil plus lactose as filler) or lactose only (placebo).

A study drug regimen involving increasing doses of pitolisant and modafinil was chosen in order to determine the best individual dosage based on clinical efficacy and tolerance criteria (individual dose titration). The dosing regimen was once daily in the morning for pitolisant, and twice daily in the morning and at noon for modafinil.

***Objectives***

The main efficacy objective was to demonstrate superiority of pitolisant compared to placebo on Epworth Sleepiness Scale (ESS) score in narcoleptic patients with Excessive daytime sleepiness (EDS) treated for 3 weeks with dose adaptation and followed by 5-week stable doses.

Secondary efficacy objectives were:

- to explore non-inferiority of pitolisant as compared to modafinil on ESS score,
- to evaluate responders rate on ESS score,
- to evaluate drug effects on daytime sleepiness via measurements including Maintenance of Wakefulness Test (MWT), patient's sleep diaries and sustained attention to response task (SART),
- to evaluate drug effects on cataplexy by measurement of frequency of cataplexy crisis on the "sleep diary".

***Outcomes/endpoints***

Primary endpoint was a comparison, using a linear mixed effect model, of the difference in ESSF between the pitolisant and placebo groups, adjusted for ESSB and using treatment and centre as fixed and random effects, respectively.

Main secondary endpoints were ESS Responder Rate ($\leq$ 10), MWT, Sustained Attention to Response Task (SART), Number/Severity of Cataplexy Attacks (Total & Partial), Clinical Global Impressions of Change (CGI-C) and European Quality of Life Questionnaire (EQ-5D).

***Sample size***

The sample size was calculated under the following hypotheses derived from historical trials; the minimum clinically relevant difference on ESSF was 3, ESS Standard Deviation assumed to be $\sigma$=5, estimated coefficient of correlation r(ESSB, ESSF) = $\rho$=0.65, and compound symmetry for the repeated measurements. The Non-inferiority Margin (NIM) was estimated by the Applicant as a small proportion of the difference between the reference and placebo and less than the minimum clinically important difference. From meta-analytical results on historical trials of modafinil this difference was $\Delta$=4.12, 95%CI [0.14, 7.09], a value of NIM=2 was considered as a relevant value. Using the power function of ANCOVA, and under the above assumptions, the sample size was determined by separately examining the two hierarchical tests: 1) A difference as large as $\Delta$=3 with the following parameters (two-sided $\alpha$=0.05, pre-visits=2, post-visits=2, r=0.65) was found detectable with a power of at least 95%, once the sample size exceeds n=30 patients/group. 2) Assuming that the two drugs have the same efficacy, the probability to reject at a pre-determined fixed margin NIM=2 associated with the following parameters ($\alpha$=0.025, pre-visits=2, post-visits=2, r=0.65) will be at least 80%, once the sample size exceeds n=30 patients/group. Thus, to satisfy the requirement of the two tests, 30 patients per group were planned.

***Randomisation***

Randomisation was centralised and performed in blocks of 6: 2 pitolisant, 2 modafinil and 2 placebo.

***Blinding (masking)***

The investigational treatments were provided as non-openable capsules that were identical in appearance to ensure that neither the patient nor the investigator or the clinical staff knew the identity of the study medication. Since it was a dose adjusted trial, the existence of “low”, “middle” and “high” packs for each treatment arm of treatment allowed up- and down-titration of treatment.

***Statistical methods***

All statistical analyses conducted for the evaluation of efficacy were performed on the EIT, IT, and PP populations.

**- IT Population** (Main selection): The Intent-to-Treat (IT) population consisted of all randomized patients having taken at least one dose of drug and provided at least one value after baseline.

**- EIT Population:** The Extended Intent-to-Treat (EIT) population consisted of all randomized patients, regardless if treatment was initiated and irrespective of their outcome.

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

Main analysis - EDS measured by ESS: The significance of the active tested drug compared with placebo was assessed by Analysis of Covariance on Final ESS adjusted for baseline ESS. ANCOVA was conducted with a Mixed Linear Model taking into account centre heterogeneity. Due to multiple comparisons of treatments, the multiplicity of type 1 error has been taken into account using a step-down approach: the two subsequent tests of superiority (pitolisant>placebo) and non-inferiority (pitolisant vs modafinil) on a fixed Non-Inferiority margin (NIM) were tested using the same alpha level.

More precisely, the non-inferiority testing was to be performed following two subsequent steps: Step 1. H01: pitolisant ≤ placebo had to be rejected at $\alpha$= 0.025. The comparison between pitolisant and modafinil was to be only assessed when H01 was rejected. Step 2: H02: pitolisant ≤ modafinil – $\theta$ ($\theta$ being the non-inferiority margin) had to be tested at the same pre-specified significance level. If both hypotheses were rejected, the gold standard non-inferiority trial should, as a general rule, be termed successful. The main ANCOVA model assumed no treatment-baseline interaction term (CPMP 2003).

Other efficacy criteria

Two-way comparisons between treatment groups were planned via ANCOVA, where baseline adjustment on associated baseline values had to be conducted where appropriate.

Parameters involving duration of time, standard survival analysis were planned with adjustment on baseline values where appropriate.

For MWT and SART, the significance of treatment difference was tested according to a Mann Whitney test, as from previous studies, the measured endpoint could not be considered as normally distributed.

The difference between placebo and pitolisant, and pitolisant and modafinil was tested by calculating absolute risk difference (and 95%CI) of the proportion of patients for which the increase of the measured endpoint from V3 to V7 exceeded a pre-determined Minimum Clinical Relevance.

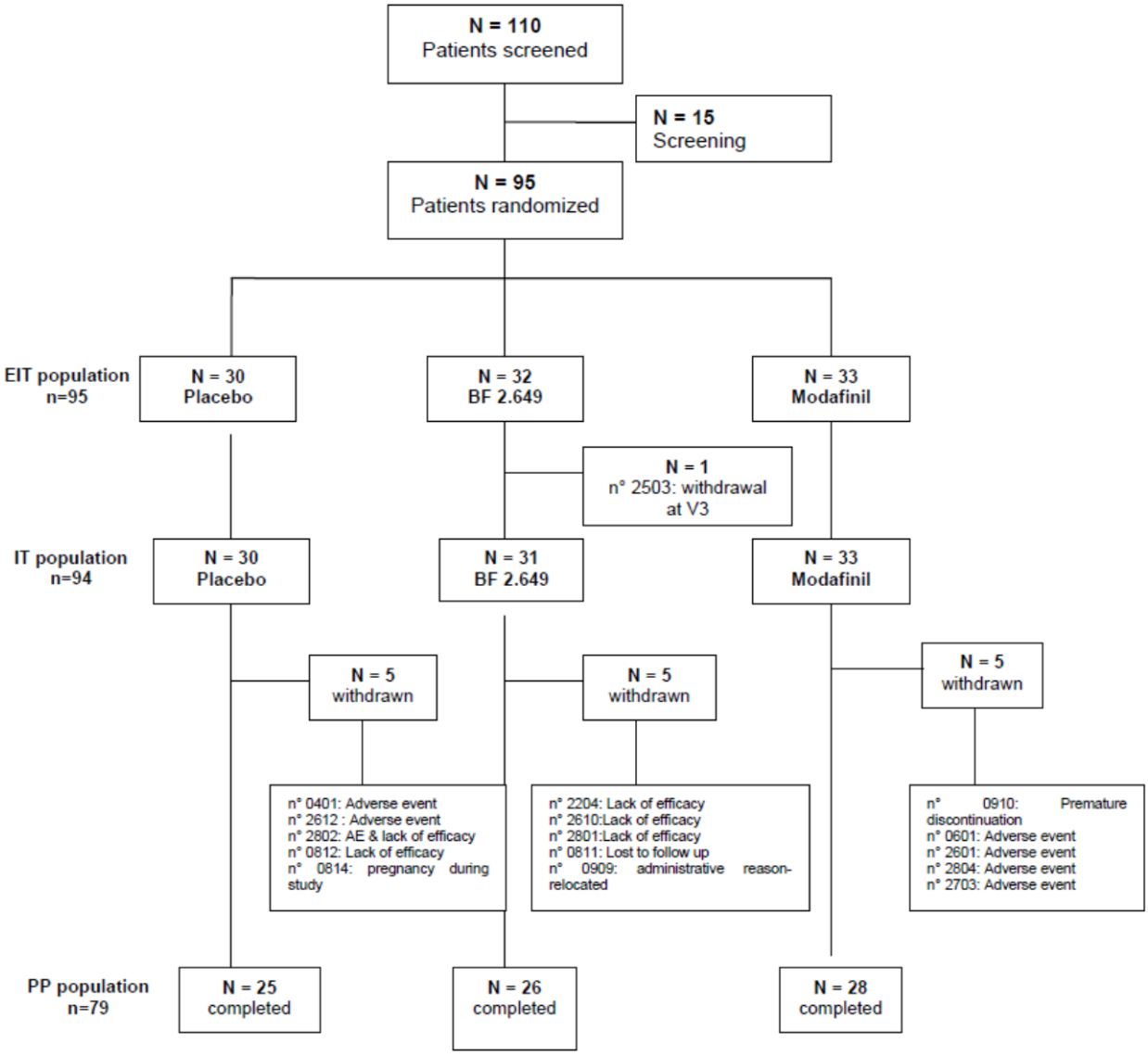
Handling of dropouts or missing data

For patients without ESS scores at V6 or V7, ESSF was the last observation carried forward (LOCF) value. Missing data for secondary endpoints were not imputed.

***Results***

**Participant flow**

**Disposition of patients in Harmony I study.**




**Recruitment**

This study was conducted in 24 centres in Europe. The first patient was enrolled on 26 May 2009 and last study visit was performed on 30 June 2010.

**Conduct of the study**

The protocol has been amended three times. The modifications included removal of the upper age limit for inclusion and modification of statistical analysis from superiority to non-inferiority versus comparator (modafinil).

**Baseline data**

There were no clinically relevant differences between groups for any of the characteristics examined. The median age of the included patients ranged from 33 to 40 years in the 3 treatment groups. More

than 90% of the population was Caucasian and approximately 50% was male, with no statistical differences between groups, as for the body weight, height and BMI.

The baseline characteristics of narcolepsy by treatment group for patients in the IT population showed no statistically significant differences for any of the parameters evaluated ($p>0.05$ for all comparisons). The median duration since the diagnosis of narcolepsy was 14.9 years in the placebo group, 10.6 years in the pitolisant group and 11.7 years in the modafinil group. 80% of the enrolled patients reported a history of cataplexy. No patients reported a history of drug abuse or dependence disorder. More than one-half of the enrolled patients reported histories of sleep paralysis, hallucinations or dyssomnia. Less than half reported automatic behaviour. A Multiple Sleep Latency Test (MSLT) was performed in 58 patients out of 94. Mean latency time at baseline seemed to be shorter in the pitolisant group ($p>0.05$). There were no statistical differences between groups on ESS, CGI-S EDS, CGI-S cataplexy, EQ-5D, SART-NOGO, SART-GO, SART-TOTAL and MWT baseline mean scores.

Patients with severe cataplexy were permitted to remain on their anticataplectic (sodium oxybate) or supposed anticataplectic medications (antidepressive drugs e.g. venlafaxine) at stable doses. Such treatments were administered for at least 1 month prior to the trial and maintained at stable dose for the duration of the trial in 33 patients. There were no statistically significant differences between treatment groups with respect to this parameter.

**Numbers analysed**

A total of 110 patients were considered eligible to participate to the study and to initiate the wash-out period. Of these, 95 were randomized to receive treatment (EIT sample). The IT population (all randomized patients having taken at least one dose of drug and provided at least one value after baseline) included all patients (30/30) from placebo group, 31 of 32 patients from pitolisant group (one patient excluded from the IT analysis since they did not take study treatment and did not go to the visits after randomization) and all patients (33/33) from modafinil group.

The PP Population (all patients in the IT population who completed the study until at least V6 and without any major protocol deviation related to primary endpoint) was composed of 25 (of 30) patients from placebo group, 26 (of 31) patients from pitolisant group and 28 (of 33) patients from modafinil group.

**Outcomes and estimation**

*Primary Efficacy Endpoint*

The mean ESSB were 18.9 ± 2.5 (SD), 17.8 ± 2.5 and 18.5 ± 2.7 in the placebo (PL), pitolisant (BF) and modafinil (MD) groups respectively (IT population). By study end, mean ESS score reductions from baseline were -3.4 ± 4.2 in the placebo group, -5.8 ± 6.2 in the pitolisant group and -6.9 ± 6.2 in the modafinil group.

The results of the primary endpoint analysis are presented in Table 8 below.

**Table 8. Efficacy analysis results for ESS scores in Harmony I study (IT, EIT, PP populations).**

| | Point Estimate Δ Adjusted ESS F * | | | | |
|---|---|---|---|---|---|
| | **PL** | **BF** | **Est.** | **95% CI** | **P** |
| IT population | 15.6 | 12.0 | -3.0 | [-5.6; -0.4] | 0.024 |
| EIT population | 15.6 | 12.3 | -3.0 | [-5.6; -0.4] | 0.024 |
| PP population | 14.8 | 10.9 | -3.7 | [-6.6; -0.9] | 0.012 |

Source data: Table 14.2.3.2 and Appendix A.1 of the S.A.R.
* mixed linear model including ESS BL and groups as fixed effects and Centers as random effect.

Results from the IT analysis of the primary endpoint showed that pitolisant was clinically and statistically significant compared to placebo (-3.33 points; 95%IC [-5.83; -0.83]; $p < 0.05$). These results were based on baseline observation carried forward analysis.

*Secondary Efficacy Endpoints*

As the analysis on primary endpoint met pre-defined criteria, showing that pitolisant was better than placebo on adjusted ESSF difference, a second analysis of non-inferiority of pitolisant with respect to modafinil was performed.

The mean difference between the two active treatments was of 0.12 (95%CI: -2.5 to 2.7), rejecting the hypothesis of non-inferiority of pitolisant compared to modafinil based on a non-inferiority margin (NIM) of 2.

The robustness of these data was confirmed when a fixed effects ANCOVA model was used on the primary endpoint in the IT and PP populations for both pitolisant vs placebo and pitolisant vs modafinil, adjusting for baseline ESS and with and without centre adjustment.

Responder rate on ESS scores (ESS $\leq$ 10 points), showed that pitolisant was significantly superior to placebo (OR=9.24 [3.82-22.35]; p<0.001), and not statistically different from modafinil (OR=1.06 [0.44; 2.54]; p=0.894), supporting results from primary endpoint.

**Table 9. Responders rate (OR pitolisant vs placebo and pitolisant vs modafinil) in Harmony I study.**

| | Odds Ratio | **IT (N=94)** | | | | |
|---|---|---|---|---|---|---|
| | **Comparison** | **Control** | **BF** | **Est.** | **95%CI** | **P** |
| ESS ≤ 10 + (Any AEs) | BF/PL | 13.3 (4) | 45.2 (14) | 9.24 | [3.82; 22.35] | <0.001 |
| | BF/MD | 45.2 (14) | 45.5 (15) | 1.06 | [0.44; 2.54] | 0.894 |

*OR = Odds Ratio of treatment responders adjusted on ESS Baseline (Logistic Regression Model).*

Superiority of pitolisant compared to placebo was also observed on MWT (objective secondary endpoint), pitolisant significantly increased wakefulness maintenance time by 1.47 min (p=0.044) compared to placebo.

The effect of pitolisant was also assessed on cataplexy in this study by measuring the daily cataplexy rate (DCR). According to the results using a reciprocal of the number of days of exposure as an imputation method, pitolisant showed statistically significant reduction of DCR compared to the placebo

(RR=0.38, 95%CI [0.16; 0.93]; p=0.034), when no significant difference was observed between pitolisant and modafinil on this parameter (RR=0.70, 95%CI [0.297; 1.629]; p=0.396).

Results from quality of life measurements (EQ5D) did not show statistically significant differences among the three arms treatment (placebo, pitolisant and modafinil), but the estimates of the differences in EQ5D of pitolisant compared to placebo and modafinil were positive (in favour of pitolisant).

The CGI-S on cataplexy was assessed by the investigator. At baseline, the CGI-S of cataplexy mean score was around 3.3 (max = 6 points) reflecting "slight to moderate" form of cataplexy and was homogeneous between all 3 therapeutic groups (p=0.440). The results of the CGI-C on cataplexy were assessed only in the patients who experienced cataplexy during the trial. There was no significant difference between treatment groups at all visits, including V7.

**Ancillary analyses**

Patients with a "stable dose" were those who received the same dose of medication from the titration visit through the final visit (last 5 weeks of treatment). In pitolisant arm, low, medium and high doses were respectively 10, 20 and 40 mg/d, and in modafinil arm 100, 200 and 400 mg/d, respectively, as shown in Table 10 below.

**Table 10. Summary of stable dose stage [% (n)] in Harmony I study.**

| Stable Dose | PLACEBO (N=30) | BF2.649 (N=31) | MODAFINIL (N=33) | TOTAL (N=94) |
|---|---|---|---|---|
| Titrated to low stable dose | 0.0 (0) | 6.5 (2) | 6.1 (2) | 4.3 (4) |
| Titrated to medium stable dose | 20.0 (6) | 25.8 (8) | 12.1 (4) | 19.1 (18) |
| Titrated to high stable dose | 76.7 (23) | 61.3 (19) | 72.7 (24) | 70.2 (66) |
| Did not receive a stable dose | 3.3 (1) | 6.5 (2) | 9.1 (3) | 6.4 (6) |

In pitolisant group, more than 60% of the patients reached and pursued the study at the stable dose of 40 mg/d, as compared to ~26% and 6.5% of patients stabilised at the doses of 20 and 10 mg/d, respectively.

When analyzing ESS results in the medium and the high stable doses groups in pitolisant population, the medium stable dose (20 mg/d) showed numerically better results on ESS scores (mean final score=8.1; reduction of 9.1 points from baseline) than the high stable dose (40 mg/d; mean final score=12.9; reduction of 5.3 points from baseline). The same trend was also seen on responder rate, where 62.5% of patients from the medium stable dose subgroup compared to 36.8% of patients from the high stable dose subgroup were considered as responders (ESS $\leq$ 10) at final visit.

**Table 11. Summary of ESS by pitolisant stable dose [Mean ± SD] in Harmony I study.**

| IT Population | BF 20mg (N=8) | | BF 40mg (N=19) | |
|---|---|---|---|---|
| **Visit** | **N** | **MN ± SD** | **n** | **MN ± SD** |
| **Baseline (BL)** | 8 | 17.3 ± 2.3 | 19 | 18.2 ± 2.8 |
| **Final (F)** | 8 | 8.1 ± 5.3 | 19 | 12.9 ± 6.1 |
| **F-BL** | 8 | -9.1 ± 5.8 | 19 | -5.3 ± 6.1 |
| **(F-BL) / BL (%)** | 8 | -51.9 ± 31.4 | 19 | -28.7 ± 30.8 |
| **Mean** | 8 | 8.6 ± 4.7 | 19 | 13.4 ± 5.4 |
| **Responders** | | **% (n)** | | **% (n)** |
| **ESS ≤ 10 + (any AEs)** | | 62.5 (5) | | 36.8 (7) |

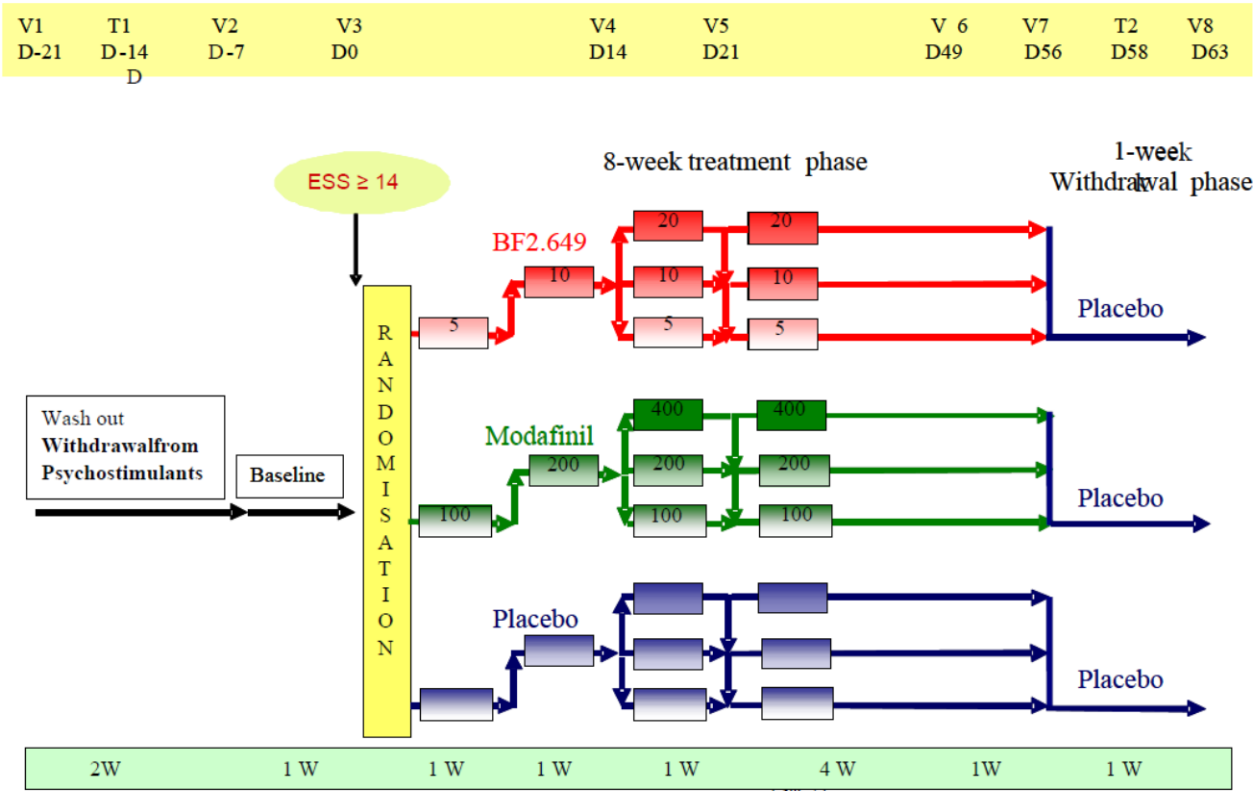
**Study 09-15 Randomized, double-blind, placebo and comparator-controlled, parallel-group, multicenter trial assessing the effects of BF2.649 in the treatment of excessive daytime sleepiness in narcolepsy (Harmony I BIS)**

***Methods***

**Study design**

The schematic representation of study design is presented in Figure 2 below

**Figure 2 Study P09-15 (Harmony Ibis) design.**



The design of Harmony Ibis study was similar to Harmony I design. The difference was the initiation dose and the maximal dose of pitolisant used the Harmony Ibis, 5 mg and 20 mg/d, respectively compared to 10 and 40 mg/d in Harmony I study.

The choice of the maximal dose of 20 mg/d was justified by the Applicant as follows:

1. a dose-range study conducted in patients with Parkinson's Disease and diurnal sleepiness showed that 20 mg OD was the minimum effective dose and its effect on ESS was not different to the effect observed with the 40 mg OD dose,
2. in Harmony I study (P07-03), one quarter of patients received the 20 mg OD dose during the 6-week stable dose phase and had their ESS score dramatically improved,
3. the comparison of results of both studies Harmony I (P07-03) and Harmony Ibis (P09-10) conducted according to similar protocols, with the exception of the dose, replaces a dose-finding study in the indication of narcolepsy.

***Study Participants***

Patient population in this study was similar to Harmony I study. The baseline ESS score had to be ≥ 14/24.

***Treatments***

Pitolisant, modafinil and placebo were provided as capsules. Each capsule contained either tablets (pitolisant or modafinil plus lactose as filler) or lactose only (placebo).

***Objectives***

The efficacy objectives were similar to those of Harmony I study: demonstrate superiority of pitolisant compared to placebo on ESS score in narcoleptic patients with EDS after 8 weeks of treatment; explore non-inferiority of pitolisant as compared to modafinil on ESS score and evaluate drug effects via measurements including MWT, SART and cataplexy rate.

***Outcomes/endpoints***

The primary and key secondary endpoints were the same as in Harmony I study.

In addition, polysomnographic (PSG) recording was performed in the sleep laboratory the night before V3 (at baseline) and before V7 (at endpoint) for the first 20 patients enrolled in three selected centres; 3 patients in the placebo group, 8 in the pitolisant group and 9 in the modafinil group. PSG was performed to evaluate the study drug effect on the different sleep parameters in patients with narcolepsy, and especially whether pitolisant could induce insomnia or sleep disturbance.

***Sample size***

The sample size was designed under a step-down analysis using the power function of ANCOVA, to assess two hierarchical tests:

a. Superiority of pitolisant compared to placebo, with a difference on ESSF of at least D=3 and the following parameters [two-sided $\alpha$ = 0.05, estimated coefficient of correlation r(ESSB, ESSF) = $\rho$= 0.7, $\sigma$=5] with a power of 95%.
b. Non-inferiority of pitolisant compared to modafinil, with a non-inferiority margin (NIM) fixed to 2 and the following parameters ($\alpha$ = 0.05, r = 0.7, $\sigma$=5).

To satisfy the requirement of the two tests, sample sizes of 20 (placebo), 40 (modafinil) and 40 (pitolisant) was suggested. A 1:2:2 randomization ratio was chosen because: a) this was a superiority test (placebo><verum), and a non-inferiority test (verum><modafinil). Because the non-inferiority

test requires more patients, the size of the placebo arm was reduced, b) the size of the two verum arms was increased. However, as non-inferiority had to be concluded both on Intent to Treat and Per Protocol bases, it was necessary to increase the sample sizes by 20%. In these conditions, the sample sizes was initially 25 (placebo), 50 (pitolisant), 50 (modafinil).

The estimation of sample size was modified following the preliminary results of Harmony I study. The Pearson Linear Coefficient Study R was evaluated at R=0.37 [95%CI 0.151 to 0.508], a value not compatible with the original assumption of R=0.7, planned in this study. This sample size was calculated on this new basis: A smaller value of R was fixed to its observed upper bound R=0.5.

As a result of these calculations, the total sample size in modafinil and pitolisant groups had to be at least 75/group and the sample size of the placebo group had to be at least 35.

***Randomisation***

Randomisation was centralized and performed via an Interactive Web Response System (IWRS) which was set up in blocks of 5: 2 pitolisant, 2 modafinil and 1 placebo. Attribution of treatments to the centres was performed by treatment units according to the randomization list.

***Blinding (masking)***

Pitolisant, modafinil and placebo were provided in sealed capsules. The capsules were identical in appearance and taste to ensure that neither the patient nor the investigator or members of the clinical staff knew the identity of the study medication. The therapeutic units were prescribed to patients in accordance with an individual titration program and the posology determined during the titration phase.

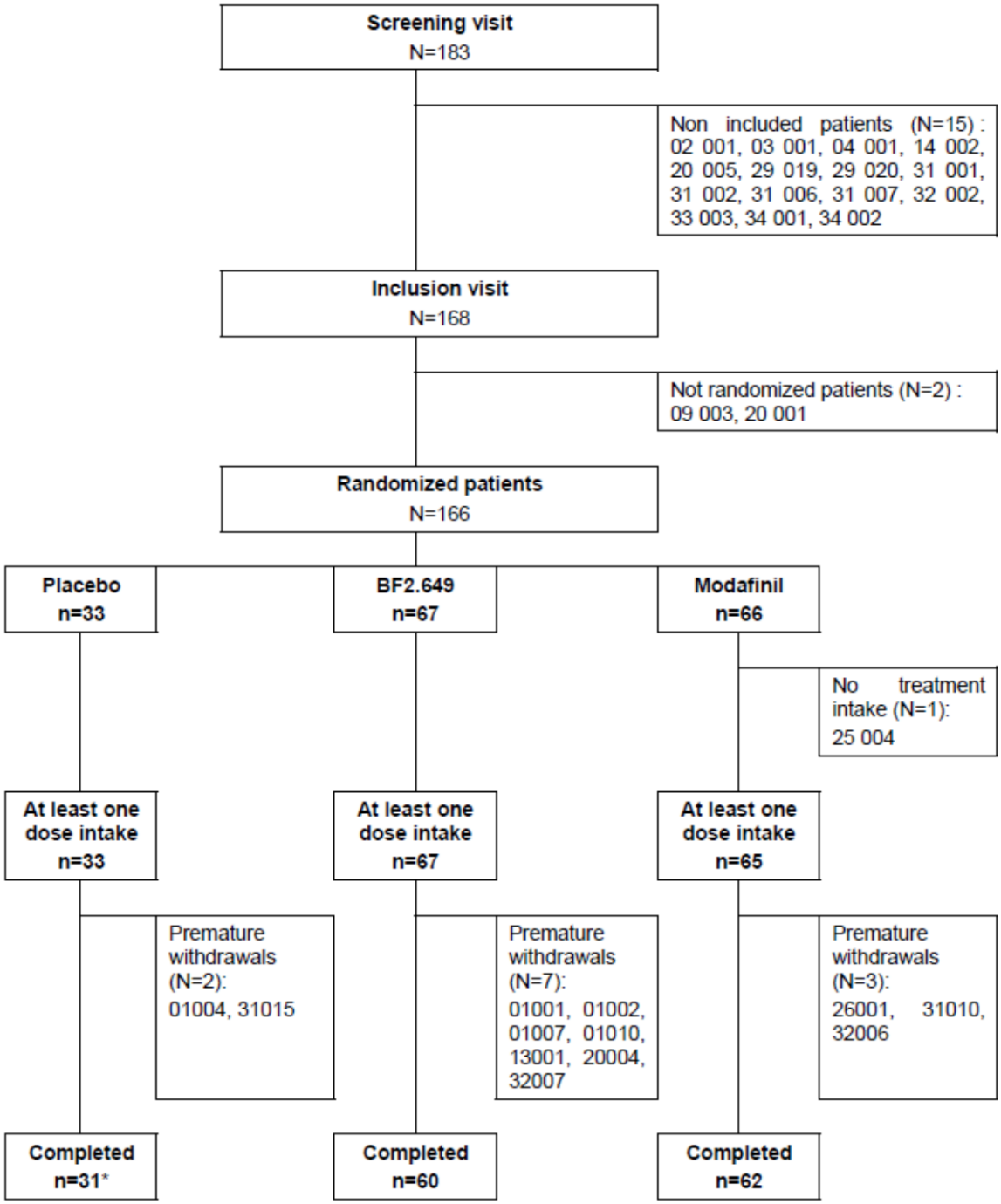
***Statistical methods***

Statistical methods were similar to those used in Harmony I study. Statistical analyses were conducted on the EIT, IT, and PP populations. For the main efficacy endpoint analysis of covariance on final ESS adjusted for baseline with treatment considered as a fixed factor and centre as a random effect was used. Superiority test of pitolisant compared with placebo and Non-inferiority test of pitolisant compared with modafinil were simultaneously tested by a hierarchical procedure (step-down approach). For the secondary efficacy endpoint logistic regression model adjusted on baseline (ESS responders), Student's t-test and geometric mean (MWT, SART), quasi-Poisson regression model (Daily Cataplexy Rate) were used.

***Results***

**Participant flow**

**Disposition of patients in Harmony Ibis study.**




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

**Recruitment**

Patients were enrolled in 26 centres in 8 countries. The first patient was enrolled in the study on October 25th, 2010; the last study visit was on July 24th, 2012.

**Conduct of the study**

The protocol has been amended on May 4th 2011. The major modifications concerned change in the planned sample size and changes regarding the analysis of patients' sleep diaries. Among the data collected by patients in their sleep diaries, only cataplexies (partial and total crisis) were analysed.

**Baseline data**

Patients included in this study were in majority Caucasian (~85%). The average age was 40 years. Around 53% of the patients were female. There was no statistically significant difference between treatment groups with regards to the baseline demographic characteristics.

The baseline characteristics of narcolepsy showed no statistically significant differences between treatment groups for any of the parameters evaluated. The time elapsed since narcolepsy diagnosis was between 0 and 62 years at baseline and was not statistically significantly different between treatment groups (median=11, 15, 10 years in the placebo, pitolisant, modafinil groups respectively; p=0.715). Mean baseline ESS score was 18 in each treatment group. The proportion of patients with history of cataplexy was between 75 and 81% and similar between treatment groups.

**Numbers analysed**

183 patients were selected, of which 166 were randomized (EIT population): 33 in the placebo group, 67 in the pitolisant group and 66 in the modafinil group.

IIT population included 164 patients. 152 patients had no major protocol violation and did not prematurely withdrew the study and therefore constitute PP population; 30 patients (93.9%) in placebo group, 60 (89.6%) in the pitolisant group and 62 (95.4%) in the modafinil group.

The number of premature withdrawals was higher in pitolisant group (n=7) compared to modafinil (n=3) and placebo groups (n=2). In pitolisant group, adverse events were main reason for a premature withdrawal (4 out of 7).

Withdrawal for lack of efficacy was limited in Harmony Ibis study (n=2): one in placebo group and the other in pitolisant group.

**Outcomes and estimation**

*Primary Efficacy Endpoint*

Mean ESS score reductions from baseline were -3.6 ± 5.6 in the placebo group, -4.6 ± 4.6 in the pitolisant group and -7.8 ± 5.9 in the modafinil group as shown in Table 12 below.

**Table 12. Summary of ESS scores [Mean ± SD] in Harmony Ibis study - IT Population.**

| IT (N=163) | | | | | | |
|---|---|---|---|---|---|---|
| | PLACEBO (N=32) | | BF2.649 (N=66) | | MODAFINIL (N=65) | |
| Visit | n | MN ± SD | n | MN ± SD | n | MN ± SD |
| Visit 1 | 26 | 16.4 ± 4.8 | 48 | 16.6 ± 3.8 | 47 | 16.0 ± 5.6 |
| Visit 2 | 20 | 18.1 ± 2.4 | 58 | 18.1 ± 2.4 | 53 | 18.2 ± 3.0 |
| Visit 3 | 31 | 18.1 ± 2.6 | 66 | 18.5 ± 2.7 | 63 | 18.3 ± 3.0 |
| Visit 4 | 31 | 15.3 ± 4.4 | 65 | 14.7 ± 5.1 | 63 | 12.8 ± 5.4 |
| Visit 5 | 31 | 14.4 ± 5.3 | 63 | 13.9 ± 5.5 | 63 | 11.0 ± 6.1 |
| Visit 6 | 30 | 14.3 ± 6.1 | 60 | 13.3 ± 5.6 | 62 | 10.5 ± 6.2 |
| Visit 7 | 29 | 14.3 ± 6.1 | 61 | 13.6 ± 5.5 | 62 | 10.4 ± 6.2 |
| Visit 8 | 29 | 14.7 ± 6.2 | 60 | 14.1 ± 5.7 | 59 | 11.7 ± 5.9 |
| Baseline (BL)* | 32 | 18.2 ± 2.3 | 66 | 18.3 ± 2.4 | 65 | 18.1 ± 2.8 |
| Final (F) ** | 32 | 14.6 ± 5.8 | 66 | 13.7 ± 5.4 | 65 | 10.3 ± 6.1 |
| F-BL | 32 | -3.6 ± 5.6 | 66 | -4.6 ± 4.6 | 65 | -7.8 ± 5.9 |
| (F-BL)/BL | 32 | -20.0% | 66 | -25.8% | 65 | -43.3% |
| Mean‡ | 32 | 14.8 ± 5.1 | 66 | 14.0 ± 5.0 | 65 | 11.2 ± 5.4 |

** ESSBL = (ESSV2 + ESSV3)/2; ** ESSF = (ESSV6 + ESSV7)/2; ‡ MEAN = Arithmetic mean across all visits between ESSBL and ESSF.*

The primary endpoint analysis showed non-significant ESS score decrease with pitolisant compared to placebo [-1.94 (-4.05, 0.07); p=0.065].

*Secondary Efficacy Endpoints*

Responder rate on ESS scores, according to responder definition in this study ("ESS final ≤ 10 points or ESS baseline – ESS final ≥ 3 points"), showed that pitolisant was significantly superior to placebo (RR=0.60 [0.41-0.88]; p=0.008).

According to MWT results, pitolisant significantly increased the maintenance of wakefulness compared to placebo (p=0.009). At final visit, the duration of the maintenance of wakefulness increased in pitolisant group (7.79 min; Δ=+1.14 min) where it decreased in placebo group (6.51 min; Δ=-1.39 min). However, the mean final MWT value in pitolisant group was still less than the threshold of normal value of 8 min.

These results were confirmed by SART scores, where the ratio of mean change between pitolisant and placebo was statistically significant (0.83; 95%CI [0.69; 0.99]; p=0.043).

When non-inferiority analysis of pitolisant compared to modafinil was performed, it was concluded that this hypothesis could not be retained, the lower bound of the 95%CI of the difference being smaller than the pre-defined non-inferiority margin of -2 points (difference=-2.75; 95%CI [-4.48 to -1.02]).

The DCR increased in this study from baseline to final visit in pitolisant group (mean pre-post difference of +0.85), but this difference was not significant between pitolisant and placebo groups. Meanwhile, in modafinil group, DCR deceased between baseline and final visit (-0.33). These results were not consistent with those observed in Harmony I study, where pitolisant performed significantly better than placebo and where modafinil was not significantly different from the placebo.

As for Harmony I study, results from quality of life measurements (EQ5D) did not show statistically significant differences among the three arms treatment (placebo, pitolisant and modafinil), but the estimates of the differences in EQ5D of pitolisant compared to placebo was positive whereas the difference compared to modafinil were negative, but the direction of the observed difference was not specified.

The results on CGI-C on EDS (significant improvement by pitolisant and modafinil compared to placebo) and CGI-C on cataplexy (non-significant change between treatment groups) were consistent with those observed in Harmony I study.

Polysomnography was not considered as an efficacy endpoint, since its aim was to evaluate if the treatment with pitolisant or modafinil impairs the sleep parameters. PSG was performed in the first 20 patients enrolled in three selected centres. The results showed that PSG parameters did not statistically significantly differ between groups at V3 and at V7. The change between V3 and V7 did not also significantly differ between groups, which suggests that pitolisant and modafinil did not impair the diurnal sleep.

**Ancillary analyses**

*Stable dose analysis*

The daily doses administered during the stable dose phase of the study are presented in Table 13.

**Table 13. Summary of stable dose stage [% (n)] in Harmony Ibis study.**

| Visit | Dose Received | PLACEBO (N=33) | BF2.649 (N=67) | | MODAFINIL (N=65) | | TOTAL (N=165) |
|---|---|---|---|---|---|---|---|
| V7 | Low | 0.0 (0) | *5mg* | 3.0 (2) | *100mg* | 3.1 (2) | 2.4 (4) |
| | Medium | 15.6 (5) | *10mg* | 23.9 (16) | *200mg* | 26.2 (17) | 23.2 (38) |
| | High | 81.3 (26) | *20mg* | 62.7 (42) | *400mg* | 66.2 (43) | 67.7 (111) |

Analysis of the stable dose range reached in pitolisant groups in both pivotal studies show that 61.3% and 62.7% of patients were on the upper stable dose of 40 mg/d and 20 mg/d in Harmony I and Ibis studies, respectively.

*Small centres reallocation*

Because there were sites where the 3 treatment groups were unbalanced, the 36 active sites were randomly assigned to 5 clusters which replaced the original sites as covariates in regression analyses.

The results of the IT analysis of the primary endpoint after small-centres reallocation showed a significant improvement of -2.19 (95%CI [-4.17 to -0.22]; p=0.030) for pitolisant compared with placebo, this difference remained similar across the IT and PP populations. This difference was not clinically relevant as it was lower than the pre-defined threshold of 3 points.

**Table 14. Summary results for primary endpoint analysis in Harmony Ibis study (IT, PP populations) after small-centre reallocation**

| Endpoint | | IT (N=163) PLACEBO (N=32) BL | FINAL | BF2.649 (N=66) BL | FINAL | MODAFINIL (N=65) BL | FINAL | PP (N=152) PLACEBO (N=30) BL | FINAL | BF2.649 (N=60) BL | FINAL | MODAFINIL (N=62) BL | FINAL |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| ESS[(1)] | Value | 18.2 | 14.6 | 18.3 | 13.7 | 18.1 | 10.3 | 18.3 | 14.5 | 18.2 | 13.4 | 18.2 | 10.6 |
| | F-BL | -3.6 ± 5.6 | | -4.6 ± 4.6 | | -7.8 ± 5.9 | | -3.8 ± 5.7 | | -4.8 ± 4.6 | | -7.6 ± 5.9 | |
| | Treat † | -2.19 [-4.17; -0.22] p = 0.030 | | -2.75 [-4.48; -1.02] p = 0.998** | | | | -2.21 [-4.32; -0.09] p = 0.041 | | | | -2.40 [-4.21; -0.58] p = 0.990** | |

*(1) **F-BL** (Mean difference between Final (F) and Baseline (BL)), and **treat** (Treatment effect adjusted following the pre-defined model).*
*†The primary analysis was conducted using a linear mixed effects model (LME), featuring analysis of covariance ANCOVA on final ESSf adjusted on ESSb, with treatment considered as a fixed factor and center as a random effect (thus hypothesis of center variability of the model intercept.*
** BF was compared with placebo with a superiority test.*
*** The comparison between BF and Modafinil on the primary analysis was with a non-inferiority test by considering the non-inferiority margin NI=-2.*

When the comparison between pitolisant and modafinil was considered regarding ESS Final scores, the primary analysis adjusted on new site clusters showed that modafinil was statistically significantly superior to pitolisant (MOD-BF2=-2.75 with p-value=0.002) and sensitivity analyses performed on the primary endpoint adjusted on original sites (MOD-BF2=-3.1 with p-value=0.0002) would even tend to demonstrate the inferiority of pitolisant compared to modafinil with clinically relevant significance.

**Table 15. Results of ESS analysis with different adjustments methods in Harmony Ibis study.**

| Type of analysis | Compared groups | Results | P value |
|---|---|---|---|
| IT adjusted ESSF with small centres reallocation | BF vs placebo | -2.19 | 0.03 |
| IT adjusted ESSF with original centres | BF vs placebo | -1.94 | 0.065 |
| IT adjusted ESSF with small centres reallocation | BF vs MD | -2.75 | 0.0021 |
| IT adjusted ESSF with original centres | BF vs MD | -3.07 | 0.0002 |

## Summary of main studies

The following tables summarise the efficacy results from the main studies 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 16. Summary of efficacy for trial 07-03 (Harmony I).**

| | | |
|---|---|---|
| **Title:** Prospective, randomized double-blind study, placebo-controlled, parallel-group, multi-center trial assessing the effects of BF2.649 in treatment of excessive daytime sleepiness in narcolepsy (Harmony I) | | |
| Study identifier | P07-03 | |
| Design | Phase III, multicenter, double blind study, randomized versus placebo and comparator (modafinil). | |
| | Duration of main phase: | 8 weeks of double blind treatment |
| | Duration of Run-in phase: | 3 weeks of wash-out |

| | | | |
|---|---|---|---|
| | Duration of Extension phase: | | Option to enter P09-10 study (Harmony III), open-label, long-term treatment (at least 12 months). |
| Hypothesis | Two subsequent steps: superiority of pitolisant compared to placebo, then non-inferiority of pitolisant compared to modafinil if pitolisant > placebo. | | |
| Treatments groups | Pitolisant up to 40 mg/d | | Oral capsule. 8 weeks, 32 randomized patients |
| | Modafinil up to 400 mg/d | | Oral capsule. 8 weeks, 33 randomized patients |
| | Placebo | | Oral capsule. 8 weeks, 30 randomized patients |
| Endpoints and definitions | Primary endpoint | ESS (Epworth Sleepiness Scale) score | Comparison, using a linear mixed effect model, of the difference in ESSF between the pitolisant group and the placebo group. |
| | Key-Secondary endpoint | Responder rate | Rate of patients with ESSF ≤10. |
| | Secondary endpoints | 1. MWT<br>2. SART<br>3. Cataplexy rate | 1 & 2. Comparison of the variation of MWT, SART-T scores from baseline to final visit between different arms.<br>3. Frequency of complete or partial cataplexy crisis recorded in the sleep diary. |
| | Other secondary endpoints | 1. CGI-C on EDS<br>2. CGI-C on cataplexy | Comparison of the variation of CGI on EDS and cataplexy scores from baseline to final visit between different arms. |
| Database lock | 22 November 2010 | | |

**Results and Analysis**

| **Analysis description** | **Primary Analysis** | | | |
|---|---|---|---|---|
| Analysis population and time point description | Mainly, IT Population (all randomized patients having taken at least one dose of drug and provided at least one value after baseline) and PP Population (all patients in the IT population who completed the study until at least V6).<br>Time point: 8 weeks of treatment. | | | |
| Descriptive statistics and estimate variability | Treatment group | Placebo | Pitolisant | Modafinil |
| | Number of subject | 30 | 32 | 33 |
| | ESSF score | 15.6 | 12.0 | 11.6 |
| | SD | 4.7 | 6.2 | 6.0 |

| | | | |
|---|---|---|---|
| Effect estimate per comparison | Primary endpoint | Comparison groups | Pitolisant (up to 40 mg/d)<br>vs.<br>Placebo |
| | | Mean difference adjusted to baseline values between groups (superiority test) | -3.33 points |
| | | 95%IC | [-5.83 to -0.83] |
| | | P-value | p < 0.05 |

| | | | |
|---|---|---|---|
| | Subsequent primary endpoint | Comparison groups | Pitolisant (up to 40 mg/d)<br>vs.<br>Modafinil (up to 400 mg/d) |
| | | Mean difference adjusted to baseline values between groups (non-inferiority test) | 0.12 points |
| | | 95%IC | [-2.5; 2.7] |
| | | Margin of non-inferiority | Defined to 2 points, non-inferiority excluded. |
| Notes | The objective of the primary efficacy analysis was to demonstrate the superiority of pitolisant up to 40 mg/d over placebo after 8 weeks of treatment (3-week titration period followed by 5-week stable dose). This aim was achieved allowing a second analysis of non-inferiority of pitolisant compared to modafinil (up to 400 mg/d) with a predefined non-inferiority margin threshold of 2 points. Since the 95%IC interval of the observed difference between the two treatments included this value [-2.5; 2.7], this hypothesis of non-inferiority of pitolisant compared to modafinil is rejected. | | |
| **Analysis description** | **Secondary analysis / Other** | | |
| Effect estimate per comparison | **Endpoints** | **Comparison groups** | **Results** |
| | Responder rate (ESS $\leq$ 10 at V7) | BF/PL | 9.24 [3.82; 22.35]<br>p<0.001 |
| | | BF/MD | 1.06 [0.44; 2.54]<br>p=0.894 |
| | MWT (V7 – V3) | BF/PL | 1.47 [1.01 ; 2.14]<br>p=0.044 |
| | | BF/MD | 0.77 [0.52 ; 1.13]<br>p=0.173 |
| | SART-TOTAL (V7 – V3) | BF/PL | 0.80 [0.64 ; 1.00]<br>p=0.053 |
| | | BF/MD | 0.90 [0.71 ; 1.14]<br>p=0.370 |
| | Cataplexy rate | BF/PL | 0.38 [0.16; 0.93]<br>p=0.034 |
| | | BF/MD | 0.70 [0.297; 1.629]<br>p=0.396 |
| | CGI-C on EDS (improvement at V7) | PL, BF, MD | 56.0%, 73.1% and 85.7%, resp.<br>p=0.053 |
| | CGI-C on cataplexy (improvement at V7) | PL, BF, MD | p=0.844 |
| Notes | Results from some secondary endpoints (responder rate, MWT and cataplexy rate) confirm positive efficacy data observed on primary endpoint. | | |

*PL=placebo; BF=pitolisant; MD=modafinil.*

**Table 17. Summary of efficacy for trial 09-15 (Harmony Ibis).**

| | | | |
|---|---|---|---|
| **Title:** Randomized, double-blind, placebo and comparator-controlled, parallel-group, multicenter trial assessing the effects of BF2.649 in the treatment of excessive daytime sleepiness in narcolepsy ("Harmony I BIS") | | | |
| Study identifier | P09-15 | | |
| Design | Phase III, prospective, randomized, double-blind, placebo and comparator (modafinil) controlled, parallel group, pivotal, multi-center study. | | |
| | Duration of main phase: | 8 weeks of double blind treatment | |
| | Duration of Run-in phase: | 3 weeks of wash-out | |
| | Duration of Extension phase: | Option to enter P09-10 study (Harmony III), open-label, long-term treatment (at least 12 months). | |
| Hypothesis | Two subsequent steps: superiority of pitolisant compared to placebo, then non-inferiority of pitolisant compared to modafinil if pitolisant > placebo. | | |
| Treatments groups | Pitolisant up to 20 mg/d | | Oral capsule, 8 weeks, 67 randomized patients |
| | Modafinil up to 400 mg/d | | Oral capsule. 8 weeks, 66 randomized patients |
| | Placebo | | Oral capsule. 8 weeks, 33 randomized patients |
| Endpoints and definitions | Primary endpoint | ESS (Epworth Sleepiness Scale) score | Comparison, using a linear mixed effect model, of the difference in ESSF between the pitolisant group and the placebo group. |
| | Key-Secondary endpoint | Responder rate | Rate of patients with ESSF ≤10 or ESS-F – ESS-B ≥ 3. |
| | Secondary endpoints | 1. MWT<br>2. SART<br>3. Cataplexy rate | 1 & 2. Comparison of the variation of MWT, SART scores from baseline to final visit between different arms.<br>3. Frequency of complete or partial cataplexy crisis recorded in the sleep diary. |
| | Other secondary endpoints | 1. CGI-C on EDS<br>2. CGI-C on cataplexy | Comparison of the variation of CGI on EDS and cataplexy scores from baseline to final visit between different arms. |
| Database lock | March 13th 2013 | | |

**Results and Analysis**

| **Analysis description** | **Primary Analysis** | | | |
|---|---|---|---|---|
| Analysis population and time point description | Mainly, IT Population (all randomized patients having taken at least one dose of drug and provided at least one value after baseline) and PP Population (all patients in the IT population who completed the study until at least V6).<br>Time point: 8 weeks of treatment. | | | |
| Descriptive statistics and estimate variability | Treatment group | Placebo | Pitolisant | Modafinil |
| | Number of subject | 32 | 66 | 65 |
| | ESSF score | 14.6 | 13.7 | 10.3 |
| | SD | 5.8 | 5.4 | 6.1 |

| | | | |
|---|---|---|---|
| Effect estimate per comparison | Primary endpoint | Comparison groups | Pitolisant (up to 20 mg/d)<br>vs.<br>Placebo |
| | | Mean difference adjusted to baseline values between groups (superiority test) | -1.94 points |
| | | 95%IC | [-4.05; -0.07]; |
| | | P-value | p=0.065 |
| | Subsequent primary endpoint | Comparison groups | Pitolisant (up to 20 mg/d)<br>vs.<br>Modafinil (up to 400 mg/d) |
| | | Mean difference adjusted to baseline values between groups (non-inferiority test) | -2.75 points |
| | | 95%IC | [-4.48; -1.02] |
| | | Margin of non-inferiority | Defined to 2 points, non-inferiority excluded. |
| Notes | The objective of the primary efficacy analysis was to demonstrate the superiority of pitolisant up to 20 mg/d over placebo after 8 weeks of treatment (3-week titration period followed by 5-week stable dose). This aim was statistically achieved after reallocation of small centers (not pre-planned analysis), but the result was below the minimum clinically relevant difference of 3 points. The second programed analysis of non-inferiority of pitolisant compared to modafinil (up to 400 mg/d) with a predefined non-inferiority margin threshold of 2 points was performed, leading to rejection of non-inferiority of pitolisant compared to modafinil (difference=-2.75; 95%IC [-4.48; -1.02]). Furthermore, when superiority test comparing pitolisant to modafinil is performed (sensitivity analysis), modafinil showed significantly (p<0.002) better results on ESS Final score (Δ=-2.75 points). | | |
| **Analysis description** | **Secondary analysis / Other** | | |
| Effect estimate per comparison | **Endpoints** | **Comparison groups** | **Results** |
| | Responder rate (ESS $\leq$ 10 at V7 or ESS-F – ESS-B $\geq$ 3) | BF/PL | 0.60 [0.41; 0.88]<br>p=0.008 |
| | | BF/MD | 0.90 [0.74; 1.10]<br>p=0.306 |
| | MWT (V7 – V3) | BF/PL | 1.57 [1.12; 2.20]<br>p=0.009 |
| | | BF/MD | 1.05 [0.80; 1.38]<br>p=0.713 |
| | SART-TOTAL (V7 – V3) | BF/PL | 0.83 [0.69; 0.99]<br>p=0.043 |
| | | BF/MD | 0.93 [0.77; 1.11]<br>p=0.407 |
| | Cataplexy rate | BF/PL | -1.00 [-2.12; 0.128]<br>p=0.077 |

| | | | |
|---|---|---|---|
| | | BF/MD | 0.05 [-0.55; 0.65] p=0.865 |
| | CGI-C on EDS (improvement at V7) | PL, BF, MD | 34.4%, 65.7% and 75.4%, resp. p=0.001 |
| | CGI-C on cataplexy (improvement at V7) | PL, BF, MD | p=0.111 |
| Notes | Analysis of secondary endpoints shows that some (responder rate, MWT, SART-Total and CGI-C on EDS) confirm positive efficacy data observed on primary endpoint. | | |

*PL=placebo; BF=pitolisant; MD=modafinil.*

**Analysis performed across trials (pooled analyses and meta-analysis)**

*Pivotal studies endpoints analysis*

The observed result on the primary endpoint (ΔESS) was clinically relevant (> 3 points) and statistically significant ($p < 0.05$) in the first study where pitolisant was used up to 40 mg/d but neither clinically relevant (around 2 points) nor statistically significant [p=0.065] in the second larger pivotal study where pitolisant was used up to 20 mg/d. To address this contradiction between results, the applicant conducted a pooled statistical analysis of the two pivotal studies based on a general Individual Patient Data Analysis model using multiple endpoint O'Brien OLS test combining ESS, MWT and SART together. This analysis showed that both low and high doses (20 and 40 mg) were better than placebo. The Z score (aggregating ESS, MWT and SART) was significant for both 20mg (Main effect Z=-0.56, 95%CI -0.86,-0.27, p<0.001), and 40mg (Main 40mg effect Z=-0.43, 95%CI 0-.83,-0.03, p=0.04). The separate analyses based on each endpoint alone (ESS, MWT, SART) provided a similar trend, even though the results were not statistically significant for 40 mg/d on ESS and MWT (p=0.3 and 0.071, respectively).

*Responder definition*

To override the inconsistency in responder definition across pivotal studies the applicant provided a post-hoc analysis of responders in both pivotal studies using both responder definitions ("ESS final ≤ 10 points" and "ESS final ≤ 10 points or ESS final – ESS baseline ≥ 3 points"). This analysis is presented in the table below and showed the same trend of responders' rate across pivotal studies regardless of responder definition.

**Table 18 Response rates (in percent %) by study and treatment.**

| | Resp1 : ESS≤10 | | Resp2=ESS≤10 or Change≥3 | |
|---|---|---|---|---|
| | H1 (40 mg) | H1bis (20 mg) | H1 (40 mg) | H1bis (20 mg) |
| Placebo | 13.3 | 21.9 | 43.3 | 43.8 |
| Pitolisant | 45.2 | 30.3 | 71.0 | 66.7 |

*Clinical relevance*

To better characterise the efficacy of pitolisant on EDS in narcolepsy, pitolisant results on ESS and MWT were compared to those of modafinil issued from 6 historical randomised controlled trails to which results from Harmony I and Ibis studies were added. Regarding ESS results, the difference between pitolisant 40mg and modafinil was -0.15, 95%CI [-2.89, 2.42], in favour of pitolisant (not statistically significant). Based on the same calculation, the difference in ESS between pitolisant 20mg

and modafinil was 0.66, 95%CI [-1.42, 2.74], at the advantage of modafinil (not statistically significant). Modafinil was characterized by mean increase over baseline of MWT weighted mean difference (positive effect) of 3.12 minutes (95%CI [2.32, 3.93], p<.001) compared with placebo. The difference in MWT between pitolisant 40mg or 20mg compared with placebo was 5.67 minutes (95%CI 0.933; 10.42) and 1.57 minutes (95%CI 1.12; 2.20), respectively. When compared to modafinil, the differences were not significant for both doses.

*Cataplexy sub-group analysis*

Patients enrolled in pivotal clinical trials were in ~80% cataplectic, which consolidated the diagnosis of narcolepsy but raised the question about the effectiveness of pitolisant in both subgroups. This issues was resolved as sub-group analysis showed no significant difference on ESS between patients with or without cataplexy.

Patients with cataplexy were allowed to use anticataplectic (sodium oxybate) or supposed anticataplectic medications (antidepressive drugs like SSRIs, venlafaxine…) at stable doses in both studies. The distribution of concomitant anticataplectic medications was homogenous among the treatment arms in both pivotal studies. The potential impact of anticataplectic treatments on overall treatment effect of EDS was raised since some anticataplectic (like sodium oxybate) have an antinarcoleptic effect. To address this point, a post-hoc analysis was conducted by the applicant showing that no additional nor interaction effect of concomitant medication with pitolisant were observed in pivotal studies (based on the results of the primary endpoint [ESS] and other secondary endpoints [MWT, SART and responders rate]).

**Supportive studies**

**Study P09-10 (Harmony III)**

This was a phase III, naturalistic, open-label, prospective, longitudinal, uncontrolled, multicenter trial to assess the long-term safety of pitolisant in the treatment of Excessive Daytime Sleepiness (EDS) in narcolepsy (prolonged follow-up).

This study enrolled patients who completed a double blind controlled study with pitolisant (Harmony I, Harmony II [prematurely stopped], Harmony Ibis, or other phase II study in narcolepsy), patients who in the opinion of the investigator would not have been able to participate in a double-blind study but could benefit from pitolisant or patients receiving pitolisant under French “ATU nominative” procedure. The study duration was 12 months.

Unbiased conclusions on efficacy from this study could not be drawn (open-label study, no reference therapy, psychostimulant concomitant treatments, association of naive and already treated patients) However, the data analysis allowed to compare the effect of pitolisant in the naturalistic study with effects observed in pivotal trials as well as confirm if this effect is maintained over a longer period.

In this study, 102 narcoleptic patients with or without cataplexy were included, aged 18 to 69 years old, with a required baseline ESS score at inclusion ≥12 (mild to severe form of disease).

The main results showed that:

- The maximal dose received during the study was 40 mg/d in 88% of patients;

- The ESS change from baseline to final visit was about -4.3 points, overall of the same magnitude of what was observed in Harmony I (-5.8 points) and Harmony Ibis (-4.6 points);

- Responders’ rate (ESS ≤ 10 or ESSF-ESSB ≥ 3) was of the same magnitude as in Harmony Ibis (68.2%), using the same definition of responders.

**P11-05 (Harmony CTP)**

This was a double-blind, randomized, parallel group study of pitolisant versus placebo in narcoleptic patients (n=105, aged 18 to 66, mean age ~36 years). The enrolled patients had a high frequency of cataplexy (geometric mean weekly cataplexy rate ~8) and a mean ESS baseline value of about 17.

The primary endpoint was the change in the average number of cataplexy attacks per week (Weekly Rate Cataplexy: WRC) between the 2 weeks of baseline (Day-14 to Day 0) and the 4 weeks of stable treatment period (D21 to D49).

Overall, the results showed a beneficial effect of pitolisant on cataplexy:

- The primary analysis on IT population showed a significant improvement in the pitolisant group at end of the stable dose treatment period. The WRC has decreased from 7.31 and 9.15 for placebo and pitolisant respectively to 6.79 and 3.28 for placebo and pitolisant respectively, with a ratio rate rR(Pt/Pb), rR=0.512 (95%CI = 0.435, 0.603, p<0.0001). These results were confirmed by a BOCF analysis.
- At the end of the treatment, the distribution of patients with very high cataplexy rate (WRC>15) was significantly different between placebo (23.5% [12/51]) and pitolisant (5.6% [3/54]) groups, in favour of pitolisant (p<0.0001).
- When analysing the effect of the stable dose received of pitolisant, - 20mg (9 patients) and 40mg (35 patients), a significant decrease on the WRC was observed with both the 20 mg (from 8.42 to 3.38) and 40 mg (from 8.46 to 3.57) stable doses - as compared to placebo (from 7.09 to 6.28), with a rR for 20 mg dose= 0.392 (95% CI 0.270, 0.571; p<0.0001), and rR for 40 mg dose= 0.623 (95% CI 0.510, 0.761, p < 0.0001).
- The CGI-C score regarding cataplexy significantly decreased with pitolisant in comparison with placebo (mean reduction -0.95; 95%CI -1.36, -0.54; p<0.0001), as well as the proportion of patients responding to treatment (CGI score ≤ 3) which was significantly greater with pitolisant (66.7%) than with placebo (33.3%) (OR=4.00; 95%CI 1.54, 10.4; p=0.004).

The results from this supportive study showed a superior efficacy of pitolisant compared to placebo on EDS symptoms assessed with the ESS scores (observed mean changes were -1.9 ± 4.3 and -5.4 ± 4.3 for placebo and pitolisant groups, respectively). The difference was statistically significant (p<0.001) and clinically relevant (the mean decrease in ESS score was above 3 units in pitolisant group).

This effect on ESS was confirmed by:

- MWT results: From baseline geometric means of 4.08 min and 3.58 min at baseline, the observed final MWTf values were 4.46 min and 6.69 min for placebo and pitolisant, respectively. The geometric mean of the ratios (MWTF/MWTB) for pitolisant compared to placebo was 1.8 (95%CI 1.19; 2.71, p=0.005);
- the proportion of responders type 1 (ESSF≤10) and 2 on ESS (ESSF≤10 or ESSF-ESSBL≥3) showing OR=3.28 (95%CI = 1.08; 9.92, p=.035) for the first and OR=4.26 (95%CI = 1.72; 10.5, p= 0.002) for the second responder type (18.0% compared with 39.2% for responders type 1 and 34.0% compared with 68.6% for responders type 2 in placebo and pitolisant groups, respectively);
- the perceived change on EDS (CGI-C), with a mean reduction of the CGI-C score of pitolisant compared with placebo was -0.99 and was statistically significant in favour of pitolisant (mean CGI-C score was 3.7±1.4 with placebo versus 2.6±1.1 with pitolisant showing a mean reduction of 0.99;; 95%CI -1.45, -0.52; p<0.0001) and patients responders (CGI-C ≤ 3 at V6

[very much, much, or minimally improved]) were 23.5% (12/51) in placebo group compared with 68.5% (37/54) in pitolisant group, with an OR=7.07 (95%CI 2.55, 19.6; p=0.0002);

- the aggregated Z-score (combining ESS and MWT), showing a final Z-score of 0.97 (SD=1.35) in pitolisant group compared with 0.22 (SD=1.29) in placebo group.

All these endpoints showed superiority of pitolisant over placebo, and the magnitude of the changes on EDS scales was comparable to those observed in Harmony I, a trial on less severely affected patients (regarding cataplexy rate, i.e. mean weekly cataplexy rate~3.5) and in which the same maximal dosage (40 mg/d) was used.

The data from this study were considered to support the data from the pivotal studies.

## 2.5.3. Discussion on clinical efficacy

**Design and conduct of clinical studies**

The design (randomized, multicentre, double-blind versus placebo and active-control) and the number of pivotal studies was considered appropriate for this application in an orphan indication.

The population chosen in the two pivotal studies was representative of primary narcoleptic population with or without cataplexy according to the International Classification of Sleep Disorders (ICSD-2; 2005). Included patients were suffering from moderate to severe forms of narcolepsy (according to ESS $\geq$ 14/24, CGI-S on EDS > 5/6 and MSLT < 5.5 min/20 min scores at baseline), and were cataplectic in ~80% of the cases.

The titration scheme adopted by the Applicant was considered acceptable based on tolerance results from study P05-03 which showed that adverse events were more frequent during the 3 first days of treatment. This finding was also confirmed by the results of the pilot study P06-06 which used the escalating dose scheme, later applied in Harmony I and Ibis studies.

The primary endpoint in the pivotal studies was the comparison of final ESS scores between pitolisant and placebo (first step), then if a superiority was approved in the first step, the comparison between pitolisant and modafinil was allowed (second step). The use of ESS score (a subjective endpoint) as primary endpoint was adequate for the assessment of excessive daytime sleepiness in narcolepsy and it has been often studied and used in earlier clinical trials with other treatments. A minimal clinically relevant difference of 3 points on final ESS scores between pitolisant and placebo groups was defined, which was appropriate according to results seen with comparators (modafinil and sodium oxybate). Since ESS is a subjective endpoint, the Applicant used the MWT (an objective criterion) as secondary endpoint in the two pivotal studies, which was suitable. Analysis of responder rate on ESS was conducted to further elucidate clinical relevance of the effects observed with pitolisant.

For the comparison between pitolisant and modafinil, a margin of non-inferiority (MNI) of 2 points was selected by the Applicant. This was done to preserve a fraction of the relative efficacy of the control active treatment as shown from historical studies. As the point estimate of the mean ESS change for modafinil was close to 4 points, a possible value of the MNI was to keep half of this value (MNI=2). This was accepted by the CHMP, especially since both tested and reference products demonstrated statistically significant advantage over placebo and the observed difference from placebo was clinically relevant.

**Efficacy data and additional analyses**

According to the pre-specified minimal clinically relevant difference in both pivotal studies, pitolisant showed an improvement on the ESS final score compared to placebo only in Harmony I study (-3.3 points), but not in Harmony Ibis (-2.19 points, with small centres re-allocation and -1.94 points with original centres). The effect of clustering did not improve the modest effect of pitolisant on ESS changes (-1.94 versus 2.19) in Harmony Ibis as it was clinically not relevant in both analysis. However, the clustering artificially improved the p value, from non-significant (p=0.07) to significant (p=0.03).

The CHMP noted that Harmony Ibis study was most likely underpowered due to improper estimations of SD (standard deviation) and R (correlation) values of ESS as well as the number of included patients which was lower than the planned one (166 instead of 188). In addition to these two factors, the use of the 20 mg/d dose, which seems to be sufficient in only a part of narcoleptic patients (almost 1/3 of them according to Harmony I study), could have been responsible for inconsistency in ESS results between pivotal studies.

When MWT results (an objective endpoint) from both studies were considered, they showed that pitolisant significantly increased wakefulness maintenance time compared to placebo in Harmony I and Harmony Ibis studies (p=0.044 and p=0.009, respectively). In the responder rate analysis in Harmony Ibis, up to 66% of pitolisant patients showed an improvement ≥ 3 points of their ESS score from baseline. These results were also confirmed by the pooled analysis on separate endpoints, suggesting that pitolisant is effective on the treatment of excessive daytime sleepiness in narcolepsy with or without cataplexy.

The additional analysis of pivotal trials was accepted by CHMP as an alternative to a three arms dose ranging study. The results of pooled analysis of the pivotal trials were not statistically significant for 40 mg/d dose for ESS and MWT, which could have been related to the sample size after pooling the patients to their final dose. The 40mg group was limited to 24 patients, whereas the 20mg sample grew up to 75 patients, with consequence on precision of the estimates and a lower power for comparing the 40mg group. The overall results showed that in a significant proportion of the patients (8/32=25% from Harmony I study), the 20mg dose could be considered as clinically relevant. However, dose needed to be increased in some patients confirming the proposed therapy strategy of escalating dose, and enabling a patient to benefit from the drug, without reaching the higher dose.

The overall results from phase 2 studies, pivotal and supportive studies and pooled statistical analysis of data, support the recommendation that the dose should be set to the lowest effective dose, depending on individual patient response and tolerance according to an up-titration scheme, without exceeding the dose of 40 mg per day. This has been reflected in the SmPC.

The results on cataplexy rates were not consistent between both pivotal studies. Although daily cataplexy rate was decreased from baseline to final visit in Harmony I study (from >0.6 crisis at baseline to <0.2 crisis in pitolisant group, significantly better than the changes observed in placebo group; RR=0.38; 95%IC [0.16; 0.93]; p=0.034), it seemed to have increased in Harmony Ibis study (from 0.84 crisis at baseline to 1.69 crisis in pitolisant group, with no statistical difference between pitolisant and placebo; p=0.077). However, the results of the supportive double-blind study (Harmony CTP) conducted in patients with high frequency of cataplexy where pitolisant was used up to 40mg/d were positive and confirmed the effect of pitolisant on cataplexy.

The non-inferiority of pitolisant compared to modafinil (according to ESS score changes) was rejected in both pivotal studies based on a non-inferiority margin of 2 points. To address this issue, the Applicant conducted a historical comparison from 6 randomised controlled trials with modafinil to which

Harmony I study were added and results from ESS and MWT in modafinil and pitolisant were compared. This analysis seems to indicate that pitolisant effect on EDS in narcolepsy, when used up to 40 mg/day, is of the same size of modafinil. When data from Harmony Ibis were added to this analysis, similar trends were observed.

The effect of pitolisant on quality of life showed a trend (positive difference without statistical significance) in favour of pitolisant compared to placebo in both pivotal studies and compared to modafinil in the first pivotal study, but in favour of modafinil in the second pivotal study.

The design of the long-term trial (Harmony III) was suitable to assess the long-term safety of pitolisant in narcolepsy but efficacy data from this study could only be considered as supportive, due to methodological limitations. Therefore, section 4.2 of the SmPC includes a recommendation that the maintenance of effect should be evaluated by the physician on regular basis.

### 2.5.4. Conclusions on the clinical efficacy

The CHMP concluded that there is sufficient evidence supporting pitolisant efficacy in treatment of narcolepsy with or without cataplexy in adults

## *2.6. Clinical safety*

Clinical safety assessment has been mainly based on the pooled data generated from narcolepsy studies, including 2 phase III studies that compared pitolisant to placebo and modafinil. Additional data from clinical trials in other indications (EDS associated with Parkinson disease, EDS secondary to OSA, epilepsy, schizophrenia, dementia and ADHD) were also submitted and evaluated.

**Patient exposure**

The clinical development program included a total of 1837 subjects. Out of these, 1385 were exposed to pitolisant (291 healthy volunteers, 1094 patients including 342 patients in the treatment of narcolepsy and 752 in other indications); 98 patients received modafinil as control drug and 354 received placebo.

Taking into account all available data in September 2015, including currently ongoing trials and compassionate use program, 2015 subjects have been exposed to pitolisant.

**Table 19. Overall exposure to pitolisant by September 2015.**

| Indications | Already included | Patients treated with pitolisant |
|---|---|---|
| **Overall clinical database** | | |
| Healthy volunteers | | 291 |
| Patients | | 1094(1) |
| **Additional ongoing clinical trials**(1) | | |
| EDS-OSA | | |
| HAROSA I | 244 | 198(2) |
| HAROSA II | 268 | 227(2) |
| **Temporary authorization of prescription** | | 295 |
| **Total** | | **2105** |

(1): Patients included in P09-10 (Harmony III) within 12-month duration. Extended follow-up is on-going.
(2): Patients included in the extension phase (open label) of the study to receive pitolisant treatment

33.1% of all patients treated with pitolisant were female and 66.9% male. This sex ratio was more balanced when only narcolepsy studies were taken into account. In this indication males represented 54.1 % of treated patients, which is representative of sex distribution in narcolepsy.

Out of 1094 patients treated by pitolisant, 781 were aged 18 to 65 years and 313 were aged over 65 years (234 subjects over 65 years and 77 subjects over 74 years). The median age was 58 years in the overall population and 36.5 years in the narcolepsy studies.

**Table 20: Age categories**

| | Age Range (year) | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | <65 | | 65-74 | | 75-84 | | >85 | | Total | |
| **Indications** | N | % | N | % | N | % | N | % | N | % |
| Narcolepsy | 325 | 95% | 14 | 4% | 3 | 1% | | | 342 | 100% |
| EDS-Parkinson | 273 | 51% | 195 | 36% | 66 | 12% | 1 | 0.2% | 535 | 100% |
| OSA | 109 | 88% | 14 | 11% | 1 | 1% | | | 124 | 100% |
| Epilepsy | 35 | 97% | 1 | 3% | | | | | 36 | 100% |
| ADHD | 32 | 100% | | | | | | | 32 | 100% |
| Lewy Body Dementia | 1 | 5% | 10 | 53% | 7 | 37% | 1 | 5% | 19 | 100% |
| Schizophrenia | 6 | 100% | | | | 0% | | | 6 | 100% |
| **Total** | **781** | 71% | **234** | 21% | **77** | 7% | **2** | 0.2% | **1094** | 100% |

The median duration of exposure to pitolisant was 84.5 days in the overall population and 64 days in narcolepsy studies (range 3 to 834 days). Cumulative duration of exposure to pitolisant was 1 year and above in 219 patients, between 6 months to 1 year in 150 and less than 6 months in 725 subjects (358 patients treated 1 month or less).

Data on long-term exposure (up to 12 months) in narcoleptic patients was available from non-pivotal study P09-10 (Harmony III). 104 patients were included and 102 took at least one dose of study treatment. 68 patients completed the first 12-month treatment period and 34 withdrew from the study prematurely.

In most studies, pitolisant was initially administered using an individual dosage titration scheme over three to four weeks. The most frequently received maximal daily dose was 20 mg (48.4% of total exposed patients) followed by 40 mg (34.8%) and 10 mg (11.3%). In narcolepsy studies, most of patients received a maximal daily dose of 40 mg (218 out of 342) whereas those receiving 20 mg mainly took part in non-narcolepsy trials (433 out of 529 vs 96 out of 342 in narcolepsy studies).

**Table 21. Overall pitolisant extent of exposure.**

| Study Id | Indication | Max duration of exposure | Pitolisant daily dose (mg) Oral route one tablet in the morning | | | | | | Total |
|---|---|---|---|---|---|---|---|---|---|
| | | | 5 | 10 | 20 | 30 | 40 | 60 | |
| P05-03 | Narcolepsy | 1 w | | | | | 22 | | 22 |
| P06-06 | Narcolepsy | 36 w | | | 3 | 1 | 22 | | 26 |
| P07-07 | Narcolepsy | 8 w | | | 2 | | 12 | | 14 |
| P07-03 | Narcolepsy | 8 w | | | 11 | | 20 | | 31 |
| P09-15 | Narcolepsy | 8 w | 1 | 17 | 49 | | | | 67 |
| P09-10 | Narcolepsy | 52 w | | 1 | 15 | | 86 | | 102 |
| P10-01 | Narcolepsy | 8 w | | 2 | 3 | | 21 | | 26 |
| P11-05 | Narcolepsy | 7 w | | 6 | 13 | | 35 | | 54 |
| P03-06 | Epilepsy | 1 d | | | 4 | | 4 | 6 | 14 |
| P04-07 | Epilepsy | 12 w | | | | 6 | 16 | | 22* |
| P05-08 | Dementia | 48 w | | | 7 | | 12 | | 19 |
| P05-07 | ADHD | 12 w | | | 7 | | 25 | | 32 |
| P04-08 | Schizophrenia | 12 w | | | | | 6 | | 6 |
| P05-05 | Parkinson | 13 w | | | | | 26 | | 26 |
| P07-02 | Parkinson | 4 w | 23 | 22 | 21 | | 20 | | 86 |
| P06-10 | Parkinson | 52 w | | 26 | 195 | | | | 221 |
| P06-11 | Parkinson | 52 w | | 26 | 176 | | | | 202 |
| P04-01 | OSA | 3 d | | | | | 12 | | 12 |
| P05-01 | OSA | 1 w | | | | | 21 | | 21 |
| P09-16 | OSA | 2 w | 23 | 24 | 23 | | 21 | | 91 |
| **Total** | | | **47** | **124** | **529** | **7** | **381** | **6** | **1094** |
| **% of total** | | | **4.3** | **11.3** | **48.4** | **0.6** | **34.8** | **0.5** | **100** |

***:** 23 patients were exposed to pitolisant. Patient n°0303 withdrew after randomization (V2), at least one treatment intake has been taken but patient did not come back at V3, therefore the compliance could not be calculated.

Regarding long-term exposure, 108 patients were treated from 6 months to 1 year at 20mg and 35 patients at 40mg; 164 patients were treated one year and above at 20mg, and 48 at 40mg.

### Adverse events

In studies conducted in narcolepsy, the percentage of patients treated with pitolisant (52.3%) who reported at least one adverse event was slightly higher compared to placebo (41.1%), and similar compared to modafinil (55.1%).

In studies conducted in other indications, the percentage of patients presenting with at least one AE was higher compared to the narcoleptic population (68.6% vs. 52.3%), and this applied also for the placebo treated population (45.7% vs. 41.1%). This might be explained by the overall longer duration of studies and older patients population with various concomitant and often severe diseases (e.g. Parkinson, OSA).

When considering all studies pooled, headache (11.4%) and insomnia (9.0%) were the most frequently reported events in patients treated with pitolisant, or placebo (7.6% and 2.9%, respectively). Gastro-intestinal AEs, in particular nausea, were also frequently observed with pitolisant but to a lesser extent.

A similar safety profile was observed when considering only pooled data from narcolepsy studies. However the percentage of patients who reported weight increase (2.9%), anxiety (3.5%), vomiting (2.3%), diarrhea (2.0%) and irritability (3.2%) were slightly more pronounced than when considering pooled data from all indications. Psychiatric disorders (21.9%) were reported more frequently with pitolisant, compared to placebo (8.9%) and modafinil (13.3%). As expected, gastro-intestinal

disorders were also more frequently reported with pitolisant (16.1%) than with placebo (8.2%). Inversely, nervous system disorders were slightly less reported with pitolisant (22.8% vs 23.5% modafinil vs 20.9% placebo).

**Table 22: Events representing 1% or more of all events reported in pitolisant treated patient. All studies pooled.**

| | Pitolisant (n=1094) 6047 patient-month | | | | Modafinil (n=98) 180 patient-month | | | | Placebo (n=484) 895 patient-month | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **TEAE** | **NE** | **PT** | **PT%** | **Inc** | **NE** | **PT** | **PT%** | **Inc** | **NE** | **PT** | **PT%** | **Inc** |
| Headache | 145 | 125 | 11,4% | 0,024 | 17 | 12 | 12.2% | 0.094 | 41 | 37 | 7,6% | 0,046 |
| Insomnia | 109 | 99 | 9,0% | 0,018 | | | | | 15 | 14 | 2,9% | 0,017 |
| Nausea | 80 | 72 | 6,6% | 0,013 | 2 | 2 | 2.0% | 0.011 | 12 | 12 | 2,5% | 0,013 |
| Back Pain | 46 | 44 | 4,0% | 0,008 | | | | | 8 | 8 | 1,7% | 0,098 |
| Depression | 36 | 33 | 3,0% | 0,006 | 1 | 1 | 1.0% | 0.006 | 4 | 4 | 0,8% | 0,004 |
| Parkinson s disease | 36 | 33 | 3,0% | 0,006 | | | | | 7 | 7 | 1,4% | 0,008 |
| Dizziness | 30 | 29 | 2,7% | 0,005 | 8 | 5 | 5.1% | 0.044 | 8 | 8 | 1,7% | 0,009 |
| Anxiety | 31 | 30 | 2,7% | 0,005 | 3 | 3 | 3.1% | 0.017 | 3 | 3 | 0,6% | 0,003 |
| Fall | 31 | 27 | 2,5% | 0,005 | | | | | 9 | 8 | 1,6% | 0,010 |
| Nasopharyngitis | 28 | 24 | 2,2% | 0,005 | 6 | 6 | 6.1% | 0.033 | 7 | 7 | 1,4% | 0,008 |
| Arthralgia | 24 | 23 | 2,1% | 0,004 | | | | | 2 | 2 | 0,4% | 0,002 |
| Fatigue | 25 | 23 | 2,1% | 0,004 | 1 | 1 | 1.0% | 0.006 | 11 | 11 | 2,3% | 0,012 |
| Pain In Extremity | 22 | 20 | 1,8% | 0,004 | 1 | 1 | 1.0% | 0.006 | 4 | 4 | 0,8% | 0,004 |
| Irritability | 25 | 24 | 2,2% | 0,004 | 3 | 3 | 3.1% | 0.017 | 2 | 2 | 0,4% | 0,002 |
| Hallucination/ Hallucination Auditory&visual | 23 | 21 | 1.9% | 0.004 | 1 | 1 | 1% | 0.006 | 6 | 6 | 1.2% | 0.007 |
| Bronchitis | 22 | 22 | 2,0% | 0,004 | 1 | 1 | 1.0% | 0.006 | | | | |
| Vomiting | 21 | 21 | 1,9% | 0,003 | | | | | 8 | 7 | 1,4% | 0,009 |
| Diarrhoea | 19 | 18 | 1,6% | 0,003 | 6 | 6 | 6.1% | 0.033 | 13 | 13 | 2,7% | 0,015 |
| Vertigo | 18 | 18 | 1,6% | 0,003 | | | | | 2 | 2 | 0,4% | 0,002 |
| Tremor | 16 | 16 | 1,5% | 0,003 | 1 | 1 | 1.0% | 0.006 | 7 | 5 | 1,0% | 0,008 |
| Dyspepsia | 16 | 15 | 1,4% | 0,003 | 2 | 2 | 2.0% | 0.011 | 4 | 4 | 0,8% | 0,004 |
| Dry Mouth | 14 | 14 | 1,3% | 0,002 | | | | | 4 | 3 | 0,6% | 0,004 |
| Abdominal Pain Upper | 14 | 13 | 1,2% | 0,002 | 3 | 3 | 3.1% | 0.017 | 2 | 1 | 0,2% | 0,002 |
| Hypertension | 15 | 15 | 1,4% | 0,002 | | | | | 5 | 5 | 1,0% | 0,006 |
| Constipation | 14 | 14 | 1,3% | 0,002 | 1 | 1 | 1.0% | 0.006 | 5 | 5 | 1,0% | 0,006 |
| Weight Increased | 14 | 14 | 1,3% | 0,002 | | | | | 2 | 2 | 0,4% | 0,002 |
| Sleep Disorder | 14 | 14 | 1,3% | 0,002 | | | | | 2 | 2 | 0,4% | 0,002 |
| Infection | 14 | 14 | 1,3% | 0,002 | | | | | 3 | 3 | 0,6% | 0,003 |
| Musculoskeletal Pain | 12 | 12 | 1.,1% | 0,002 | | | | | 3 | 3 | 0,6% | 0,003 |
| Abdominal Pain | 11 | 11 | 1,0% | 0,002 | 4 | 4 | 4.1% | 0.022 | 2 | 2 | 0,4% | 0,002 |
| Influenza | 11 | 11 | 1,0% | 0,002 | 3 | 3 | 3.1% | 0.017 | 5 | 5 | 1,0% | 0,006 |
| Urinary Tract Infection | 11 | 11 | 1,0% | 0,002 | | | | | 5 | 5 | 1,0% | 0,006 |
| Rhinitis | 12 | 12 | 1,1% | 0,002 | 1 | 1 | 1.0% | 0.006 | 3 | 3 | 0,6% | 0,003 |
| Dyskinesia | 11 | 10 | 0,9% | 0,002 | | | | | 2 | 2 | 0,4% | 0,002 |
| Influenza Like Illness | 12 | 12 | 1,1% | 0,002 | | | | | 2 | 2 | 0,4% | 0,002 |
| Balance Disorder | 11 | 10 | 0,9% | 0,002 | 1 | 1 | 1.0% | 0.006 | 2 | 2 | 0,4% | 0,002 |

NE: Number of TEAE; PT: number of patients; PT% % of patient. Incidence (Inc) number of TEAE by patient-months

**Table 23: Events representing 1% or more of all events reported in pitolisant treated patient. All narcolepsy studies pooled.**

| | Pitolisant (n=342) 1710 patients treated months | | | | Modafinil (n=98) 180 patients treated months | | | | Placebo (n=158) 257 patients treated months | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | **NE** | **PT** | **PT%** | **Incidence** | **NE** | **PT** | **PT%** | **Incidence** | **NE** | **PT** | **PT%** | **Incidence** |
| Headache | 66 | 55 | 16,1% | 0,039 | 17 | 12 | 12.2% | 0.094 | 23 | 20 | 12,7% | 0,089 |
| Insomnia | 28 | 26 | 7,6% | 0,016 | | | | | 3 | 3 | 1,9% | 0,012 |
| Nausea | 19 | 19 | 5,6% | 0,011 | 2 | 2 | 2.0% | 0.011 | 5 | 5 | 3,2% | 0,019 |
| Weight Increased | 11 | 10 | 2,9% | 0,006 | | | | | 2 | 2 | 1,3% | 0,008 |
| Anxiety | 12 | 12 | 3,5% | 0,007 | 3 | 3 | 3.1% | 0.017 | | | | |
| Depression | 8 | 8 | 2,3% | 0,005 | 1 | 1 | 1.0% | 0.006 | | | | |
| Vomiting | 8 | 8 | 2,3% | 0,005 | | | | | | | | |
| Irritability | 12 | 11 | 3,2% | 0,007 | 3 | 3 | 3.1% | 0.017 | 1 | 1 | 0,6% | 0,004 |
| Diarrhoea | 8 | 7 | 2,0% | 0,005 | 6 | 6 | 6.1% | 0.033 | 3 | 3 | 1,9% | 0,012 |
| Dizziness | 8 | 8 | 2,3% | 0,005 | 8 | 5 | 5.1% | 0.044 | 4 | 4 | 2,5% | 0,016 |
| Back Pain | 8 | 8 | 2,3% | 0,005 | | | | | 1 | 1 | 0,6% | 0,004 |
| Nasopharyngitis | 7 | 7 | 2,0% | 0,004 | 6 | 6 | 6.1% | 0.033 | 1 | 1 | 0,6% | 0,004 |
| Hallucination/ Hallucination auditory&visual | 6 | 6 | 1.8% | 0.004 | 1 | 1 | 1% | 0.006 | | | | |
| Decreased Appetite | 6 | 5 | 1,5% | 0,004 | | | | | | | | |
| Arthralgia | 4 | 4 | 1,2% | 0,002 | | | | | | | | |
| Vertigo | 4 | 4 | 1,2% | 0,002 | | | | | | | | |
| Dry Mouth | 4 | 4 | 1,2% | 0,002 | | | | | 1 | 1 | 0,6% | 0,004 |
| Abdominal Pain Upper | 4 | 3 | 0,9% | 0,002 | 3 | 3 | 3.1% | 0.017 | | | | 0,000 |
| Abdominal Pain | 4 | 4 | 1,2% | 0,002 | 4 | 4 | 4.1% | 0.022 | 1 | 1 | 0,6% | 0,004 |
| Gastrooesophageal Reflux Disease | 4 | 4 | 1,2% | 0,002 | | | | | | | | |
| Cataplexy | 4 | 4 | 1,2% | 0,002 | 2 | 2 | 2.0% | 0.011 | 2 | 2 | 1,3% | 0,008 |

NE: Number of TEAE; PT: number of patients; PT% % of patient. **Incidence** number of TEAE by patient-months

Numbers of reported AEs according to pitolisant daily dose support a dose-dependence in all narcolepsy studies pooled (20.3% at 10mg; 32.5% at 20mg; 36.4% at 40mg). Most common AEs appeared to be more frequently reported with the higher pitolisant daily dose (40 mg). Other possible dose-relation was observed in overall pooled studies for 20mg and 40mg for headache, insomnia, nausea, anxiety, irritability, abdominal pain upper and weight increased. However, no clear dose-relation was observed for 10 mg and 20 mg for majority of reported AEs, in particular for GI disorders.

**Table 24: frequency of reported AEs according to pitolisant dose. All studies pooled.**

| | 10 mg (n=774) | | | 20 mg (n=743) | | | 40 mg (n=375) | | | Total (n=1094) | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | TEAE | PT | PT% | TEAE | PT | PT% | TEAE | PT | PT% | TEAE | PT | PT% |
| Headache | 25 | 24 | 3% | 48 | 46 | 6% | 55 | 47 | 13% | 145 | 125 | 11% |
| Insomnia | 25 | 23 | 3% | 48 | 46 | 6% | 26 | 24 | 6% | 109 | 99 | 9% |
| Nausea | 24 | 22 | 3% | 31 | 29 | 4% | 19 | 18 | 5% | 80 | 72 | 7% |
| Back Pain | 19 | 18 | 2% | 19 | 18 | 2% | 6 | 6 | 2% | 46 | 44 | 4% |
| Depression | 4 | 4 | 1% | 24 | 22 | 3% | 6 | 6 | 2% | 36 | 33 | 3% |
| Parkinson s disease | 15 | 14 | 2% | 19 | 17 | 2% | 1 | 1 | 0% | 36 | 33 | 3% |
| Fall | 7 | 6 | 1% | 20 | 18 | 2% | 4 | 3 | 1% | 31 | 27 | 2% |
| Anxiety | 3 | 3 | 0% | 11 | 10 | 1% | 11 | 11 | 3% | 31 | 30 | 3% |
| Dizziness | 11 | 11 | 1% | 12 | 11 | 1% | 4 | 4 | 1% | 30 | 29 | 3% |
| Nasopharyngitis | 12 | 10 | 1% | 14 | 12 | 2% | 1 | 1 | 0% | 28 | 24 | 2% |
| Arthralgia | 6 | 6 | 1% | 13 | 13 | 2% | 3 | 3 | 1% | 24 | 23 | 2% |
| Irritability | 5 | 5 | 1% | 6 | 6 | 1% | 9 | 9 | 2% | 25 | 24 | 2% |
| Fatigue | 8 | 8 | 1% | 14 | 13 | 2% | 3 | 3 | 1% | 25 | 23 | 2% |
| Bronchitis | 7 | 7 | 1% | 10 | 10 | 1% | 2 | 2 | 1% | 22 | 22 | 2% |
| Hallucination / Hallucination Auditory&visual | 3 | 3 | 0.4% | 14 | 13 | 1.7% | 5 | 4 | 1.1% | 23 | 21 | 1.9% |
| Pain In Extremity | 6 | 6 | 1% | 15 | 13 | 2% | 1 | 1 | 0% | 22 | 20 | 2% |
| Vomiting | 5 | 5 | 1% | 8 | 8 | 1% | 3 | 3 | 1% | 21 | 21 | 2% |
| Diarrhoea | 9 | 9 | 1% | 9 | 9 | 1% | 1 | 1 | 0% | 19 | 18 | 2% |
| Vertigo | 4 | 4 | 1% | 8 | 8 | 1% | 5 | 5 | 1% | 18 | 18 | 2% |
| Tremor | 5 | 5 | 1% | 9 | 9 | 1% | 1 | 1 | 0% | 16 | 16 | 1% |
| Dyspepsia | 4 | 3 | 0% | 6 | 6 | 1% | 4 | 4 | 1% | 16 | 15 | 1% |
| Dry Mouth | 4 | 4 | 1% | 5 | 5 | 1% | 4 | 4 | 1% | 14 | 14 | 1% |
| Abdominal Pain Upper | 2 | 2 | 0% | 4 | 4 | 1% | 7 | 6 | 2% | 14 | 13 | 1% |
| Hypertension | 4 | 4 | 1% | 8 | 8 | 1% | 3 | 3 | 1% | 15 | 15 | 1% |
| Constipation | 3 | 3 | 0% | 7 | 7 | 1% | 3 | 3 | 1% | 14 | 14 | 1% |
| Weight Increased | 1 | 1 | 0% | 4 | 4 | 1% | 8 | 7 | 2% | 13 | 12 | 1% |
| Sleep Disorder | 2 | 2 | 0% | 7 | 7 | 1% | 5 | 5 | 1% | 14 | 14 | 1% |
| Infection | 1 | 1 | 0% | 11 | 11 | 1% | | | 0% | 14 | 14 | 1% |
| Musculoskeletal Pain | 2 | 2 | 0% | 10 | 10 | 1% | 10 | 10 | 3% | 12 | 12 | 1% |

**NB: Total population exhibits all TEAEs within all doses of pitolisant (i.e. 5, 10, 20, 30, 40, 60mg).**

Common TEAEs in narcoleptic patients

The number of treatment-emergent adverse events (TEAE) and number of patients reporting TEAE is reported in table below:

**Table 25. Number of TEAE and number of narcoleptic patients reporting TEAE**

| | Pitolisant (n=342) 1710 patient-months | | | | Modafinil (n=98) 180 patient-months | | | | Placebo (n=158) 257 patient-months | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | **NE** | **PT** | **PT%** | **Inc** | **NE** | **PT** | **PT%** | **Inc** | **NE** | **PT** | **PT%** | **Inc** |
| TEAE | 472 | 179 | 52.3% | 0,276 | 138 | 54 | 55.1% | 0.767 | 136 | 65 | 41.1% | 0,529 |
| Serious TEAE | 17 | 13 | 3.8% | 0,010 | 2 | 2 | 2.0% | 0.011 | 2 | 2 | 1.3% | 0,008 |
| Severe TEAE | 55 | 40 | 11.7% | 0,032 | 12 | 12 | 12.2% | 0.067 | 7 | 7 | 4.4% | 0,027 |
| ADR | 276 | 138 | 40.4% | 0,161 | 77 | 38 | 38.8% | 0.428 | 65 | 32 | 20.3% | 0,253 |
| Serious ADR | 2 | 1 | 0.3% | 0,001 | | | | | | | | |
| Severe ADR | 26 | 18 | 5.3% | 0,015 | 7 | 7 | 7.1% | 0.039 | 1 | 1 | 0.6% | 0,004 |
| TEAE leading to discontinuation | 31 | 17 | 5% | 0,018 | 7 | 5 | 5.1% | 0.039 | 9 | 5 | 3.2% | 0,035 |
| TEAE leading to death | 0 | 0 | | | 0 | 0 | | | 0 | 0 | | |

NE: Number of TEAE; PT: number of patients; PT% % of patient. Incidence (Inc) number of TEAE by patient-months

The most frequent TEAES reported in narcoleptic patients were:

**Table 26 Most frequent TEAEs reported in narcoleptic patients**

| | Pitolisant (n=342) 1710 patients treated months | | | | Modafinil (n=98) 180 patients treated months | | | | Placebo (n=158) 257 patients treated months | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | **NE** | **PT** | **PT%** | **Incidence** | **NE** | **PT** | **PT%** | **Incidence** | **NE** | **PT** | **PT%** | **Incidence** |
| Headache | 66 | 55 | 16,1% | 0,039 | 17 | 12 | 12.2% | 0.094 | 23 | 20 | 12,7% | 0,089 |
| Insomnia | 28 | 26 | 7,6% | 0,016 | | | | | 3 | 3 | 1,9% | 0,012 |
| Nausea | 19 | 19 | 5,6% | 0,011 | 2 | 2 | 2.0% | 0.011 | 5 | 5 | 3,2% | 0,019 |
| Weight Increased | 11 | 10 | 2,9% | 0,006 | | | | | 2 | 2 | 1,3% | 0,008 |
| Anxiety | 12 | 12 | 3,5% | 0,007 | 3 | 3 | 3.1% | 0.017 | | | | |
| Depression | 8 | 8 | 2,3% | 0,005 | 1 | 1 | 1.0% | 0.006 | | | | |
| Vomiting | 8 | 8 | 2,3% | 0,005 | | | | | | | | |
| Irritability | 12 | 11 | 3,2% | 0,007 | 3 | 3 | 3.1% | 0.017 | 1 | 1 | 0,6% | 0,004 |
| Diarrhoea | 8 | 7 | 2,0% | 0,005 | 6 | 6 | 6.1% | 0.033 | 3 | 3 | 1,9% | 0,012 |
| Dizziness | 8 | 8 | 2,3% | 0,005 | 8 | 5 | 5.1% | 0.044 | 4 | 4 | 2,5% | 0,016 |
| Back Pain | 8 | 8 | 2,3% | 0,005 | | | | | 1 | 1 | 0,6% | 0,004 |
| Nasopharyngitis | 7 | 7 | 2,0% | 0,004 | 6 | 6 | 6.1% | 0.033 | 1 | 1 | 0,6% | 0,004 |
| Hallucination/ Hallucination auditory&visual | 6 | 6 | 1.8% | 0.004 | 1 | 1 | 1% | 0.006 | | | | |
| Decreased Appetite | 6 | 5 | 1,5% | 0,004 | | | | | | | | |
| Arthralgia | 4 | 4 | 1,2% | 0,002 | | | | | | | | |
| Vertigo | 4 | 4 | 1,2% | 0,002 | | | | | | | | |
| Dry Mouth | 4 | 4 | 1,2% | 0,002 | | | | | 1 | 1 | 0,6% | 0,004 |
| Abdominal Pain Upper | 4 | 3 | 0,9% | 0,002 | 3 | 3 | 3.1% | 0.017 | | | | 0,000 |
| Abdominal Pain | 4 | 4 | 1,2% | 0,002 | 4 | 4 | 4.1% | 0.022 | 1 | 1 | 0,6% | 0,004 |
| Gastrooesophageal Reflux Disease | 4 | 4 | 1,2% | 0,002 | | | | | | | | |
| Cataplexy | 4 | 4 | 1,2% | 0,002 | 2 | 2 | 2.0% | 0.011 | 2 | 2 | 1,3% | 0,008 |

NE: Number of TEAE; PT: number of patients; PT% % of patient. **Incidence** number of TEAE by patient-months

**Serious adverse event / deaths / other significant events**

In narcolepsy studies, 17 serious AEs were reported by 13 patients. All were considered by investigators as unrelated to studied treatment except for a case of miscarriage where causality was noted as possible. No deaths were reported.

In other pitolisant studies, 68 serious AEs (including 3 cases of death unrelated to the study drug) were reported in 56 patients. For 4 cases (psychosis, one case of syncope, one case of anxiety, one case of weight decreased) causality was assessed as possible, 3 cases (abdominal pain, one case of constipation and one case of general physical condition abnormal) as not very likely and one case of syncope noted as unlikely.

Other significant AEs

- Neuropsychiatric AEs

The most frequent reported neuropsychiatric AEs were headache, insomnia, depression, irritability, anxiety, dizziness, vertigo and malaise.

o Depression

When considering the pooled safety database (all indications), 41 events of depression were reported (4 with placebo, 1 with modafinil, 36 with pitolisant). Most of these events came from Parkinson studies (29 out of 41).

Depression was reported by 2.3% (n=8) of patients treated by pitolisant for narcolepsy, which is higher than observed for modafinil (1.0%; n=1) or placebo (0.8% all indications; 0% narcolepsy). In Harmony III study, in five cases a causal relationship with pitolisant cannot be totally excluded. In addition to data from pooled studies, article by Leu et al; 2014, described 2 patients in French ATU procedure with emerging depressive ideation under pitolisant: one with suicidal ideation after one week with 5mg/day and another with onset of sadness, low self-esteem and pessimism after 18 months with 40mg/day. Symptoms stopped one to two weeks after pitolisant was withdrawn.

o Anxiety/irritability

Compared to placebo, a higher proportion of patients treated with pitolisant experienced irritability (0.6% vs 3.2% in narcolepsy studies) and anxiety (0% vs 3.5% in narcolepsy studies). Both adverse events seemed to be dose dependent (0.8% at 20 mg and 2.4% at 40 mg for irritability in all indications studies; 1.3% at 20mg and 2.9% at 40mg for anxiety in all indications studies).

o Headache/insomnia

In the clinical program, headache (11.4% vs 7.6% placebo) and insomnia 9.0% (versus 2.9% placebo) were the most frequently reported AEs with pitolisant. These AEs were mainly mild to moderate in severity (81% and 90% respectively), and appear to be likely dose-dependent. Improvement occurred in majority of cases after dose reduction. Most of them resulted in a favourable outcome without sequelae (headache 93% and insomnia 72%).

- Gastrointestinal AEs

Pitolisant induces histamine release onto central vomiting center, and induces an increase of stomach acidity that may explain the number of TEAEs reported within the SOC “gastrointestinal disorders” during clinical studies (18.6% vs 10.7% for placebo). In clinical trials (all indications) in addition to nausea (6.6% of all pitolisant-treated patients), vomiting (1.9% of all pitolisant-treated patients) and diarrhoea (1.6% of all pitolisant-treated patients), gastric disorders caused by hyperacidity adverse effects included mainly dyspepsia (1.4% of patients in all indications), gastro-oesophageal reflux disease (1.2% of narcoleptic patients) and abdominal pain upper (1.2% of all pitolisant-treated

patients) and in lesser extent (less than 1% of all pitolisant-treated patients), hyperacidity, oesophageal burn, stomach discomfort, and abdominal discomfort. These effects were mostly mild to moderate in intensity, and none were serious. Two were severe but the patients fully recovered.

- Cardiovascular AEs

Among all pitolisant-treated patients, cardiac disorders were representing 2.1% versus 1.7% for pitolisant and placebo groups respectively. Hypertension was reported in 15 patients (1.4%), including one serious case in Parkinson P06-10 study. It was considered unrelated as the AE occurred 3 days after last drug intake.

All 8 serious cardiovascular events were reported in Parkinson studies (P06-10, P06-11 and P07-02) and were considered unlikely or unrelated, except for one case of lypothymia malaise that occurred after an effort.

In Harmony III (P09-10) 10.8% of patients (n=11) had ongoing cardiovascular disease (hypertension, right branch block, mitral valve prolapsus, cardiac rhythmic disorders) at study inclusion. Analysis of data in this sub-group of 11 patients does not identify specific safety signal, even though in the case of mild sinus bradycardia causality of pitolisant cannot be totally excluded.

- Effects on weight and appetite

No clear pattern on weight effect could be determined from available clinical data, as weight increase (2.9% in narcolepsy studies vs 1.3% placebo vs 0% modafinil), but also to a lesser extent weight decrease, have been observed in patients treated with pitolisant in clinical studies. Increased appetite was also reported in some patients but was not always associated with weight increase and or inversely. A dose-dependence for weight increase seemed to be observed in all pooled studies (1.86% at 40mg vs 0.54% at 20mg vs 0.13% at 10mg).

In study Harmony I, weight changes between last visit under allocated treatment and baseline did not differ statistically between groups. An incremental moderate increase in mean weight (kg) was observed between baseline V3 and end of treatment V7 in all groups, +3.7kg, +1.6kg and +0.2kg in placebo, pitolisant and modafinil groups respectively.

**Table 27 Body weight changes in study P07-03 (HARMONY I)**

| | | PLACEBO (N=30) | | Pitolisant (N=31) | | MODAFINIL (N=33) | | |
|---|---|---|---|---|---|---|---|---|
| **Weight (kg)** | **Visit** | **N** | **Mean ± SD** | **N** | **Mean ± SD** | **N** | **Mean ± SD** | **P-value** |
| **Baseline** | **V3** | 28 | 81.6 ± 21.2 | 28 | 91.3 ± 21.7 | 30 | 81.4 ± 18.0 | 0.116 |
| | **V4** | 27 | 82.0 ± 21.3 | 29 | 91.9 ± 22.2 | 30 | 82.5 ± 16.8 | 0.114 |
| | **V5** | 26 | 80.4 ± 20.3 | 27 | 91.8 ± 22.5 | 29 | 82.1 ± 16.7 | 0.083 |
| | **V6** | 25 | 84.9 ± 21.5 | 25 | 92.5 ± 23.5 | 26 | 83.1 ± 17.2 | 0.244 |
| **End of treatment period** | **V7** | 23 | 85.3 ± 21.1 | 26 | 92.9 ± 23.1 | 26 | 81.6 ± 17.7 | 0.142 |
| **End of one week placebo** | **V8** | 24 | 84.0 ± 18.9 | 25 | 93.5 ± 23.2 | 28 | 82.2 ± 16.9 | 0.092 |

Data from phase II study P06-06 are rather in favour of a weight increase after continuous exposure as during all three phases of this study a statistically significant weight increase was identified (+0.9kg at the end of the initial 1 month treatment, p-value = 0.094; +1.4kg at the end of 3-month extension phase, p-value = 0.080; +3.7kg at the end of 9-month extension phase, p-value = 0.025). In addition, in long-term P09-10 study, a weight increase considered possibly or likely related to the study drug, except for one, was reported in 5.9% of patients.

- Withdrawal symptoms

The occurrence of an amphetamine-like withdrawal syndrome during the 1-week wash-out period following abrupt discontinuation of treatment, was assessed through an amphetamine-like withdrawal questionnaire which stated the presence of a series of symptoms according to DSM4 i.e. dysphoria accompanied by at least 3 symptoms among: fatigue, insomnia, psychomotor agitation, increase appetite and vivid unpleasant dreams.

This questionnaire was used in 4 Phase III narcolepsy studies [P07-03 (HARMONY I), P09-15 (HARMONY Ibis), P10-01 (HARMONY IV), P11-05 (HARMONY CTP)] to investigate the withdrawal symptoms in patients treated with pitolisant, defined according to the DSM-IV.

In these 4 narcoleptic studies: 1 patient (0.6%) in pitolisant group (add-on sodium oxybate), 2 patients (1.5%) in placebo group and 4 patients (4.1%) in modafinil group reported amphetamine-like withdrawal syndrome. Because of one patient treated with pitolisant reporting amphetamine-like withdrawal symptoms, and because long term treatment did not include sufficient number of patients, withdrawal symptoms could not be excluded.

An amphetamine-like withdrawal symptoms questionnaire was also used in Parkinson studies (P06-10, P06-11). In both studies none of the patients treated with pitolisant presented an amphetamine-like withdrawal syndrome since none of them displayed dysphoria.

**Laboratory findings**

Laboratory parameters' abnormalities observed through the clinical program did not raise any particular safety signal.

No evidence of signal with regards to lipids abnormalities could be raised from available data, nevertheless it should be noted that TG and total cholesterol measurements were made only in studies P04-07 (epilepsy), P09-16 (OSA), and P09-15 (narcolepsy). These measurements in all studies would have been particularly justified as being overweight is a frequent co-morbidity in narcoleptic patients, and could be associated with dyslipidemia.

In study Harmony I (P07-03) there was a higher proportion of patients in the pitolisant group with abnormal levels of eosinophils compared to placebo and modafinil groups, at V1 (respectively 16.1% vs 6.7% and 6.1%, p-value=0.454) and at V7 (respectively 16.1% vs 6.7% and 0%, p-value=0.027). The four cases with abnormal levels of eosinophils under pitolisant treatment were described as hypoeosinophilia. This was not associated with any specific adverse events.

No clinically relevant changes in systolic and diastolic blood pressure, or in heart rate, have been detected in narcolepsy studies. A total of ECG 8289 recordings were assessed from the studies in all indications. The longest QTcF value from any Phase III study was 462 msec. There was no QTcF greater than 500 msec after manual adjudication and the largest change from baseline in the QTcF interval was 50 msec. Thus, no signal on QT prolongation was identified based on ECGs performed during the clinical development program.

**Safety in special populations**

The safety analysis in specific subgroups including elderly, or patients with renal impairment or hepatic impairment, did not reveal any relevant specific safety concerns with pitolisant, except for the frequency of insomnia that was slightly higher for elderly.

An analysis of most common AEs according to age groups could not be performed in narcolepsy studies as only 8 patients were older than 65 years. When considering OSA, Parkinson and Dementia populations treated with pitolisant, no significant difference between age groups emerged except for a

slightly higher number of reported insomnia noticed in patients aged over 75 years (8.8% vs 5.7% for 66-75 years group, vs 5.6% for 18-65 years group) which is expected for this age group.

The main exclusion criteria across the clinical trial development program included paediatric population, pregnant and/or breast feeding women, population with severe renal or hepatic impairment or with any other significant abnormality in the physical examination or clinical laboratory results, Thus, these populations were considered as “missing information” in the RMP and will be closely monitored.

**Safety related to drug-drug interactions and other interactions**

The review of the frequency of events reported in the different subgroups of patients with concomitant treatments in long-term study Harmony III P09-10 did not show any difference in the pitolisant safety profile as compared with the overall study population, with the exception of a greater frequency of insomnia in the subgroup of patients taking concomitant modafinil.

**Discontinuation due to adverse events**

In narcolepsy studies, the discontinuation rate due to AE occurrence was similar for pitolisant treated patients (5%), and modafinil treated patients (5.1%) and lower in the placebo arm (3.2%). The rate of discontinuation due to AE was higher in non-narcoleptic populations (12% and 4.9% in pitolisant and placebo treated patients respectively).

Insomnia, headache, nausea, anxiety, vertigo and depression were the most frequent adverse events causing pitolisant discontinuation.

**Post marketing experience**

Not applicable.

## 2.6.1. Discussion on clinical safety

Pitolisant is the first inverse agonist/antagonist H3R to be introduced in clinics, thus its safety profile could not be directly compared with drugs from similar pharmacologic class. The safety data seem exhaustive as they were collected from subjects who participated in all pitolisant clinical studies.

Even if all treated populations have been taken into consideration for the analysis of the safety profile of pitolisant, it could be expected to be different in narcoleptic and non-narcoleptic patients, in relation with the background disease. Therefore, clinical safety assessment for this application was mainly based on pooled data generated from clinical trials in narcolepsy. The number of patients receiving pitolisant in this indication was low, but acceptable considering that narcolepsy is an orphan disorder (0.026% of the general population).

The number of patients treated for narcolepsy long-term appears limited, in particular in study P09-10 (Harmony III) where only 10 patients received a 20 mg daily dose and 87 received the 40 mg daily dose. Data from this 12 months study showed an occurrence of TEAEs/ADRs mainly within the first 6 months. There was a small increase in the proportion of patients reporting in the period 1-3 months as opposed to up to 1 month, both for TEAE or for ADR. It was difficult to analyse the type of adverse events with delayed reporting (i.e. after a month of treatment) although it might have been linked to “headache” and “anxiety”. These adverse events seem to subside in the periods 6-9 months and 9-12 months. More importantly, no such temporal effect could be seen for severe and serious AE and it seemed to be related to treatment with the lower dose of 20 mg. Although these data are reassuring, it does not detract from the fact that the safety database for pitolisant is limited. The number of

patients treated for one year or more at the recommended dose is limited which has consequences for the evaluation of the safety as the numbers reported in this response are equally low in each time subgroup. Therefore, definite conclusion cannot be drawn on pitolisant long-term safety and it was noted as missing information in the RMP. In the opinion of CHMP, the impact of uncertainties regarding long-term safety profile in the overall benefit-risk balance of pitolisant justifies a PASS that should be an obligation for marketing authorisation and adequately designed to further characterize pitolisant in real conditions of use.

Headache and insomnia constituted a frequent cause of permanent or temporary treatment interruption. Headache, that was reported with a similar frequency in pitolisant and placebo treated patients, does not constitute an important safety concern and is identified as a common associated symptom of narcolepsy [Billiard 2006]. A statement in the SmPC that a reduced daily dose or discontinuation should be considered if symptoms persist has been introduced.

Insomnia is a potential side-effect for any psychostimulant drug with a long half-life. Considering pitolisant half-life of 8-11 hours, this adverse effect is expected. In controlled clinical trials no patient developed insomnia with modafinil (0%) compared to 6 with pitolisant (6.6%). This is unexpected as in these studies pitolisant appeared to be less effective than modafinil on vigilance, particularly in study Harmony Ibis. The frequency of insomnia was slightly higher in elderly which is expected in this sub-population.

The difference between modafinil and pitolisant, apart from the distinct mechanisms of action, may rely upon the shorter half-life of modafinil which results in twice daily administration. Pitolisant can be administered once per day, which could be a positive factor for compliance. Pitolisant-related insomnias are presumably related to its potent activation of wake promoting neurons. Nevertheless, insomnia is adequately considered as an important identified risk in the RMP and its preventability is based on dosage reduction, as stated in the SmPC.

The possible effects of pitolisant on weight and appetite are unclear. Weight increase did not appear to be systematically associated in clinical trials with appetite increase. However, there seemed to be a dose relationship for weight increase with a reporting of 0.13% for the 10mg dose, 0.54% with the 20mg and 1.86% with the 40mg dose. A possible dose effect is also suggested by data related to TEAEs by SOC in narcoleptic patients, with 7 weight increased with pitolisant 40mg vs 3 cases with pitolisant 20mg.

It was seen mainly in the first three months of treatment and seemed to stabilize thereafter. Although the changes were seen mainly in women and early after the start of treatment, the weight increase was seen over a longer time period in men. No particular concern has been raised in the obese patients.

The weight increased in patients with an increase of 5% body weight and above was 7.6 % +/- 2.7% but no clear effect on body weight could be seen, which was made more difficult by the low numbers in the database and the maximum of 52 weeks treatment duration.

When considering long-term study Harmony III, the mean body weight from all narcoleptic patients remained stable during the pitolisant treatment period. In this study, the Applicant identified seventeen patients with medical history associated with risk factors. Most frequent medical risk factors included depression or anxiety (9/17), however no conclusion could be drawn as these risk factors were associated with either increase of decrease in body weight.

In addition to pooled data from submitted clinical trials, according to publication from Leu et al, 2014, 14% of 78 narcoleptic patients treated by pitolisant in French ATU program experienced increased appetite and weight gain. The observed weight gain was progressive over time and ranged from 2 to

15kg after 2 years of treatment. However, all patients with weight gain had been previously treated by methylphenidate, mazindol or D-amphetamine and have reported anorexia under these treatments.

As tendency for increased weight is intrinsic to narcolepsy, causal relationship with pitolisant is difficult to establish. However, despite no clear patterns shown in clinical trials, weight increase was a detected AE and has been included in section 4.8 of the SmPC. In addition, the CHMP recommended including a warning in section 4.4 for treatment of patients with severe obesity or severe anorexia and need for re-evaluation in case of significant weight changes.

Uncertainty remains on the risk of depression/anxiety under pitolisant treatment as psychiatric AEs represent frequent comorbidities in narcolepsy that make analysis of causal relationship difficult. Narcolepsy is associated with a high prevalence of self-reported depressive symptoms [Mosko, 1989]. The prevalence of moderate to severe depression or anxiety ranged from 15% to 37% in the narcoleptic population [Vandeputte, 2003].

Anxiety, a possible depressive symptom, has been reported in some patients with depression and is considered as an important identified risk in the proposed RMP. Consequently, anxiety has been included as an important identified risk in the RMP. The SmPC states that a reduced daily dose or discontinuation should be considered if symptoms persist.

The Applicant has paid a special attention to detect potential impact on depression, and used the Beck Depression Inventory instrument (BDI) to assess patients' mood in majority of studies. No significant changes in BDI scores were detected in pitolisant-treated patients. However, bearing in mind the neurochemical action of pitolisant, equal attention should also be paid on the risk of switch in mood polarity in patients with bipolar affective disorder. Uncertainties remain also on a potential anxiety or depression aggravation in population with severe anxiety, severe depression (BDI $\geqslant$ 16) with suicidal risk (item G BDI > 0) excluded from the clinical trial program, and which will be potentially treated by pitolisant in real conditions of use.

In addition, pitolisant appears to be a sigma-1 agonist. Therefore, an antidepressant activity is theoretically plausible in humans. However, based on clinical data, a relationship between treatment with pitolisant and depressive symptoms cannot be excluded, therefore the risk of depression has been considered as an important identified risk in the RMP and will be further characterized through the PASS by regular evaluation of BDI score during medical visit. Section 4.4 of the SPC was also amended to recommend administering Wakix with caution in patients with history of psychiatric disorders such as severe anxiety or severe depression with suicidal risk ideation.

Consideration should be made on the concomitant exposure of pitolisant and antidepressants. Antidepressants used for cataplexy (e.g. SSRIs), and anxiolytic drugs are frequently prescribed in narcoleptic patients. In Harmony III study, 14% of patients were treated for depression or anxiety (3.9% of patients took SSRIs and 3.9% took venlafaxine). According to publication by Leu et al, 2014 concomitant use of antidepressant was observed in 24 % patients with individual ATU procedure. Thus, a probable frequent concomitant exposure to antidepressants and pitolisant is expected in real conditions of use.

SSRIs are potent inhibitors of CYP2D6, pitolisant is a substrate and a weak inhibitor of CYP2D6. The inhibition of CYP2D6 by paroxetine could lead to 2-fold increase of pitolisant exposure. Given the safety profile of pitolisant from phase II and III trials, it can be concluded that co-administration of pitolisant with inhibitors of CYP2D6 should be done with caution.

Dizziness, vertigo and malaise were reported slightly more frequently with pitolisant than with placebo but were not serious. In the narcoleptic patients starting the treatment at the dose of 40mg in study P05-03, two malaises were severe but recovered. The potential public health impact could be considered to be low since it is recommended to start the treatment progressively. Patients with

abnormal levels of sleepiness who take pitolisant should be advised that their level of wakefulness may not return to normal. Patients with excessive daytime sleepiness, including those taking pitolisant should be frequently reassessed for their degree of sleepiness and, if appropriate, advised to avoid driving or any other potentially dangerous activity.

The adverse event of “fall” was reported more often in studies in non-narcoleptic patients. Data has been provided regarding specific adverse events occurring in patients 65 years of age and older. However this data was difficult to interpret as comparison to the placebo or modafinil group has not been discussed.

As there are very few data on pregnancy (4 cases with a known outcome) and the lack of breast feeding data, no clinical conclusion can be drawn regarding pregnancy and lactation. However, based on the reprotoxicity results (concerning fertility, abortions, pre and post-natal losses, malformations, agalactorrhea, delay in development, etc.) observed in non-clinical studies at maternotoxic doses but with low or no margin of safety (at the NOAEL), the CHMP has introduced a number of precautionary measures.

Pitolisant is not recommended during pregnancy and in women of childbearing potential not using effective contraception in accordance with the Guideline on risk assessment of medicinal products on human reproduction and lactation: from data to labelling (EMEA/CHMP/203927/2005). Moreover, as pitolisant/metabolites could reduce the effectiveness of hormonal contraceptives, the CHMP proposed to advise an alternative method of contraception and to upgrade the level of recommendation to avoid pregnancy during treatment with pitolisant.

A duration of contraception measures after treatment discontinuation has been added in section 4.6 of the SmPC, based on the worst case scenario; taking into account 7 times the highest elimination half-life (t½) of pitolisant, ie 7*24h (= 7 days). Nevertheless, because uncertainties remain regarding the PK of metabolites of pitolisant an additional washout period should be considered and the Applicant has been asked to commit to update this duration when the results of the post-approval PK investigations are available.

The CHMP also recommended that as pitolisant and its metabolites are excreted in milk, it should be contra-indicated during breast-feeding. “Fertility disorders” and “Exposure during pregnancy and/or lactation” have been classified as “important potential risk” in the RMP and will be closely monitored post approval.

In addition to their presence in cerebral neurons supporting effect on vigilance, H3-receptors are found in non-histaminergic neurons in brain as well as in lungs and in the gastrointestinal tract. Consequently, in addition to psychiatric and neurologic AEs, special attention has been paid to potential pulmonary and GI AEs. Based on non-clinical results, pro-convulsive potential, cardiac toxicity (QT prolongation) and dependence potential were also considered particularly pertinent to analyze in the clinical safety assessment.

The effects of pitolisant on the gastric ulcer formation were investigated in the rat and did not show any effect. No ulcer lesions were reported as TEAEs. However, such events were not specifically searched for as no systemic endoscopy was performed during the clinical development. In addition, long-term data are insufficient to conclude on the absence of this risk after prolonged pitolisant exposure. Thus, uncertainties remain regarding gastric ulcer formation after pitolisant long-term exposure. The CHMP requested that this issue should be further characterized through the PASS.

Gastric disorders caused by hyperacidity have been considered an important identified risk in the RMP. With regards to this risk preventability, SPC section 4.4. and 4.8 state that a corrective treatment with H2-receptor antagonist or proton pump inhibitor could be initiated if these effects persist, and that

pitolisant should be administered with caution in patients with acid related gastric disorders or when co-administered with gastric irritants such as corticosteroids or NSAID.

Special consideration for pulmonary and respiratory events has been made as histamine H3R receptors are also expressed in the lungs. Their stimulation might inhibit pulmonary neurogenetic and inflammatory process. Among all pitolisant-treated patients, pulmonary and respiratory events were not reported as representing 1% or more of all events. All serious respiratory events reported with pitolisant occurred in Parkinson patients. Thus, available data from clinical studies are rather reassuring with regards to a potential effect of pitolisant on lung.

In narcolepsy clinical trials, no AEs of convulsions or seizures were reported. In epilepsy P04-07 clinical trial conducted in 22 patients, one patient prematurely discontinued pitolisant treatment because of a moderate and intermittent increase and modification of seizures. Although the investigator felt this event was doubtfully related to study drug, (as such events are frequent in pharmacoresistant epilepsy), a causal relationship for pitolisant cannot be totally excluded.

A pro-convulsive potential was observed in safety pharmacology studies conducted in mice as well as in toxicity studies performed in mice, rats and monkeys (see Non-clinical section), thereby supporting the inclusion of a warning in the SmPC section 4.4 regarding administration of pitolisant to epileptic patients.

*In vitro* studies showed that pitolisant might exert inhibitory effects on potassium channel and calcium channel (HERG currents) at high concentrations. The safety margins are however high enough to consider a limited QT prolongation potential in humans at therapeutic doses. ICH E14 TQT study in healthy volunteers, where moderate QT/QTc were observed, supported an effect on the QT at supra-therapeutic doses (120mg). Effects of pitolisant on QTcF interval at supra-therapeutic doses are confirmed by results from the Phase I study additionally submitted by the Applicant. In this study (ICH E14 analysis), following pitolisant doses of 160 mg, 200 mg and 240 mg, the ΔΔQTcF was >5 ms at the three 3 doses, with a 95% upper bound of the predicted effect above 10 ms (11.9, 13.3 and 9.9 ms respectively), that is comparable and even higher than for the positive control moxifloxacin (10.7 ms).

In Phase III pivotal studies no specific cardiac safety signal was identified, in particular with regards to QT prolongation based on ECG performed during the studies. However, the CHMP noted that exclusion criteria included patients with unstable cardiovascular illness, patients with a known history of long QTc syndrome or presenting any significant serious abnormality of the ECG or QTc interval strictly higher than 450ms. These populations excluded in clinical trials are not contra-indicated for pitolisant use in the SmPC and will be potentially exposed to pitolisant in real conditions of use.

Thus, based on available pre-clinical and clinical data, potential for QT interval prolongation has been considered as an important potential risk in the RMP. The SmPC section 4.4 has been updated to minimize this risk to patients with cardiac disease, co-medicated with other QT-prolonging drugs or known to be at risk of repolarization disorders. Patients should be also monitored in clinical situations which could result in pitolisant reaching supra-therapeutic doses, e.g. patients co-medicated with drugs that significantly increase pitolisant Cmax and AUC ratio or patients with severe renal or moderate hepatic impairment.

With regards to abuse and dependence potential of pitolisant, although self-administration study in monkeys suggested that pitolisant has reinforcing properties, no abuse study was performed according to the Guidance for Industry “Assessment of abuse potential of drugs” (January 2010). No significant effect was seen on cognition following treatment with pitolisant for up to 9 months and no significant difference was seen with patients receiving modafinil. As no data is available over a longer period, uncertainty remains on long-term procognitive effect. Given pitolisant’s pharmacological properties

(CNS stimulant, increasing dopamine release in prefrontal cortex) and capacities to increase memory performance and the duration of acquisition of animals, abuse and dependence liability could not be excluded. Consequently, “Drug abuse and misuse” and “Drug dependence” were included as important potential risks in the RMP. It is recommended that pitolisant should be administered by a physician experienced in the treatment of sleep disorders but currently available data do not warrant a need for special medical prescription.

In addition, despite the lack of signal in 4 narcolepsy clinical trials (Harmony I, Ibis, IV and CTP), where amphetamine-like withdrawal syndrome was investigated through questionnaires, the risk of withdrawal syndrome cannot be excluded as withdrawal symptoms not associated with dysphoria were observed in Parkinson studies and as one withdrawal syndrome was observed in narcoleptic study in add-on to sodium oxybate (Harmony IV).

The review of the frequency or events reported in the different subgroups of patients with concomitant treatments in long-term study Harmony III P09-10 did not show any difference in the pitolisant safety profile as compared with the overall study population, with the exception of a greater frequency of insomnia in the subgroup of patients taking concomitant modafinil.

From the safety database all the adverse reactions reported in clinical trials have been included in the Summary of Product Characteristics.

### 2.6.2. Conclusions on the clinical safety

The safety profile of pitolisant is consistent with its mechanism of action and is considered acceptable in the treatment of narcolepsy with or without cataplexy. No major safety concern was identified in the clinical trials and adverse events can be often managed by individual dose adaptation.

As narcolepsy is an orphan disease, the clinical studies included a small number of patients. Consequently, their ability to detect rare adverse reactions, or to detect adverse reactions due to prolonged exposure was low. Some uncertainties remain with regards to pitolisant’s effects on depression, weight and appetite, ulcer formation, and more generally on adverse events that might occur after long-term exposure. These considerations justify a long-term safety study in narcoleptic patients for the recommended 20 and 40mg doses. Therefore, the CHMP considers the following measures necessary to address issues related to safety:

The Applicant will conduct a Post-Authorisation Safety Study in order to further investigate the long term safety of Wakix in the treatment of narcolepsy in adult patients.

## *2.7. Risk Management Plan*

The CHMP received the following PRAC Advice on the submitted Risk Management Plan:

The PRAC considered that the risk management plan version 3 could be acceptable if the applicant implements the changes to the RMP as described in the PRAC endorsed PRAC Rapporteur assessment report.

The applicant implemented the changes in the RMP as requested by PRAC.

The CHMP endorsed the Risk Management Plan version 4 (release data: November 12, 2015) with the following content:

***Safety concerns***

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

***Pharmacovigilance plan***

| Study/activity Type, title and category (1-3) | Objectives | Safety concerns addressed | Status (planned start) | Date for submission of interim or final reports (planned or actual) |
|---|---|---|---|---|
| Required PASS<br>Category 1; non interventional | Investigate Long term safety profile in narcoleptic patients | Long term safety<br>Patients with severe depression and severe anxiety | Protocol submitted to PRAC Sep-2015<br>Start : 3Q-2016 | Final results 2023 |
| Required Mass balance; categoty 3, interventional | Assess the mass balance recovery, metabolite profile and metabolite identification of [14C]-pitolisant, at steady-state conditions, in healthy CYP2D6 phenotyped subjects. | CYP2D6 polymorphism | Planned to start in April-2016 | 2016 |
| Required, Pharmacokinetic interaction, category 3, interventional | To evaluate the PK interaction of pitolisant with sodium oxybate and modafinil in healthy male volunteers | "Pharmacokinetic interactions" | End study: Nov-2015 | 2016 |
| Required, Pharmacokinetic interaction, category 3, interventional | DDI with<br>• CYP3A4 substrates (midazolam)<br>• CYP2B6 substrates (bupropion)<br>• UGT2B7 inhibitor (probenecide) | "Pharmacokinetic interaction" | Planned to start in Q1 2016 | 2016 |

***Risk minimisation measures***

**Identified Risks**

| Safety concern | Routine risk minimisation measures | Additional risk minimisation measures |
|---|---|---|
| Insomnia | SmPC section 4.8<br>The most frequent adverse drug reactions (ADRs) reported with pitolisant were insomnia (8.4%).<br>*Insomnia*: During clinical studies, episodes of headache and insomnia have been reported (7.7 % to 8.4%). Most of these adverse reactions were mild to moderate. If symptoms persist a reduced daily dose or discontinuation should be considered. | None proposed |
| Gastric disorders with hyperacidity | SmPC section 4.8<br>The most frequent adverse drug reactions (ADRs) reported with pitolisant was Dyspepsia (1.0%) and abdominal pain upper (0.9%).<br>*Gastric disorders* caused by hyperacidity have been reported during clinical studies in 3.5% of the patients receiving pitolisant. These effects were mostly mild to moderate. If they persist a corrective treatment with proton pump inhibitor could be initiated.<br>SmPC § 4.4<br>Gastric disorders reactions have been reported with pitolisant, therefore it should be administered with caution in patients with acid related gastric disorders (see section 4.8) or when co-administered with gastric irritants such as corticosteroids or NSAID. | |
| anxiety | SmPC § 4.8<br>SmPC section 4.8: The most frequent adverse drug reactions (ADRs) reported with pitolisant was anxiety (2.1%).<br>SmPC § 4.4:<br>Pitolisant should be administered with caution in patients with history of psychiatric disorders such as severe anxiety or severe depression with suicidal ideation risk. | None proposed |
| Depression | SmPC § 4.4<br>Pitolisant should be administered with caution in patients with history of psychiatric disorders such as severe anxiety or severe depression with suicidal ideation risk.<br>SmPC § 4.8<br>Depression is listed as a common adverse event (1.3%). | None proposed |
| Weight increase | SmPC § 4.4<br>Pitolisant should be administered with caution in | None proposed |

| Safety concern | Routine risk minimisation measures | Additional risk minimisation measures |
|---|---|---|
| | patients with severe obesity or severe anorexia (see section 4.8). In case of significant weight change, treatment should be re-evaluated by the physician.<br>SmPC § 4.8<br>Weight increase is identified as one of the most frequent adverse events (0.9%). | |
| Adverse effects as a result of increased exposure in patients with<br>• Patients with impaired hepatic function<br>• renal impairment<br>• co-administration with CYP2D6 inhibitors | SmPC §4.2<br>In patients with moderate hepatic impairment (Child-Pugh B) two weeks after initiation of treatment, the daily dose can be increased without exceeding a maximal dose of 18 mg (see section 5.2).<br>Pitolisant is contra-indicated in patients with severe hepatic impairment (Child-Pugh C) (see section 4.3).<br>In patients with renal impairment, the maximum daily dose should be 18 mg.<br>No dosage adjustment is required in patients with mild hepatic impairment.<br>SmPC §4.3<br>Severe hepatic impairment (Child-Pugh C) is contraindicated.<br>SmPC §4.4<br>Pitolisant should be administered with caution in patients with either renal impairment or moderate hepatic impairment (Child-Pugh B) and dosing regimen should be adapted according to section 4.2.<br>SmPC §4.5<br>Co-administration of pitolisant with paroxetine significantly increases pitolisant mean $C_{max}$ and $AUC_{0-72h}$ ratio about 47% and 105%, respectively. Given the 2-fold increase of pitolisant exposure, its coadministration with CYP2D6 inhibitors (e.g. paroxetine, fluoxetine, venlafaxine, duloxetine, bupropion, quinidine, terbinafine, cinacalcet) should be done with caution. A dosage adjustment during the combination could eventually be considered.<br>SmPC section 5.2<br>In patients with impaired renal function (stages 2 to 4 according to the international classification of chronic kidney disease, i.e. creatinine clearance between 15 and 89 ml/min), $C_{max}$ and AUC tended to be increased by a factor of 2.5 without any impact on half-life (see section 4.2).<br>In patients with mild hepatic impairment (Child-Pugh A), there was no significant changes in pharmacokinetics compared with normal healthy volunteers. In patients with moderate hepatic impairment (Child-Pugh B), AUC increased by a | None proposed |

| Safety concern | Routine risk minimisation measures | Additional risk minimisation measures |
|---|---|---|
| | factor 2.4, while half-life doubled (see section 4.2).<br>Pitolisant pharmacokinetics after repeated administration in patients with hepatic impairment has not been evaluated yet. | |

## Potential risks

| Safety concern | Routine risk minimisation measures | Additional risk minimisation measures |
|---|---|---|
| **Proconvulsive potential** | SmPC section 4.4<br>Convulsions were reported at high doses in animal models (see section 5.3). In clinical trials, one epilepsy aggravation was reported in one epileptic patient. Caution should be taken for patients with severe epilepsy.<br>SmPC section 5.3<br>After 1 month in mice, 6 months in rats and 9 months in monkeys, no adverse effect level (NOAEL) were 75, 30 and 12 mg/kg/day, p.o., respectively, providing safety margins of 9, 1 and 0.4, respectively when compared to the drug exposure at therapeutic dose in human. In rats, transient reversible convulsive episodes occurred at $T_{max}$, that may be attributable to a metabolite abundant in this species but not in humans. In monkeys, at the highest doses, transient CNS-related clinical signs including emesis, tremors and convulsions were reported. At the highest doses, no histopathological changes were recorded in monkeys, and rats presented some limited histopathological changes in some organs (liver, duodenum, thymus, adrenal gland and lung); Juvenile toxicity studies in rats revealed that the administration of pitolisant at high doses induced a dose related mortality and convulsive episode that may be attributable to a metabolite abundant in rat but not in humans. | |
| Drug abuse and misuse | SmPC 4.2<br>Treatment should be initiated by a physician experienced in the treatment of sleep disorders<br>SmPC §5.3<br>In preclinical studies, drug dependence and drug abuse liability studies were conducted in mice, monkeys and rats. However, no definitive conclusion could be drawn on tolerance, dependence and self-administration studies. | None proposed |
| Drud dependence | SmPC 4.2<br>Treatment should be initiated by a physician experienced in the treatment of sleep disorders<br>SmPC §5.3<br>In preclinical studies, drug dependence and drug abuse liability studies were conducted in mice, monkeys and rats. However, no definitive conclusion could be drawn on tolerance, dependence and self-administration studies. | None proposed |
| Rebound effect | SmPC 4.2 | None proposed |

| Safety concern | Routine risk minimisation measures | Additional risk minimisation measures |
|---|---|---|
| | Treatment should be initiated by a physician experienced in the treatment of sleep disorders<br>SmPC § 4.4<br>During clinical trials no rebound effect was reported. However, the limited patient data does not allow for a definitive conclusion. | |
| Fertility, exposure during pregnancy and lactation | SmPC §4.3<br>Breastfeeding is contraindicated<br>SmPC §4.6<br>Women of childbearing potential<br>Women of childbearing potential have to use effective contraception during treatment and at least up to 7 day after treatment discontinuation (based on pitolisant half-life), but because of uncertainties about metabolites, as a precautionary measure, an additional 7-days washout period should be applied. Pitolisant/metabolites may reduce the effectiveness of hormonal contraceptives. Therefore, an alternative method of effective contraception should be used if the woman patient is using hormonal contraceptives (see section 4.5).<br>Pregnancy<br>There are no or limited amount of data from the use of pitolisant in pregnant women. Studies in animals have shown reproductive toxicity, including teratogenicity. In rats, pitolisant/metabolites were shown to cross the placenta (see section 5.3).<br>Pitolisant should not be used during pregnancy unless the potential benefit outweighs the potential risk for foetus.<br>Breast-feeding<br>Animal study has shown excretion of pitolisant/metabolites in milk. Therefore, breastfeeding is contra-indicated during treatment with pitolisant (see section 4.3).<br>Fertility<br>Study in animals has shown effects on semen parameters, without a significant impact on reproductive performance in males and reduction on the percentage of live foetuses in treated females (see section 5.3).<br>SmPC §5.3<br>Teratogenic effect of pitolisant was observed at matemally toxic doses (teratogenicity safety margins of <1 in rats and in rabbits). At high doses, pitolisant induced sperm morphology abnormalities and decreased motility without any significant effect on fertility indexes in male rats and it | None proposed |

| Safety concern | Routine risk minimisation measures | Additional risk minimisation measures |
|---|---|---|
| | decreased the percentage of live conceptuses and increased post-implantation loss in female rats (safety margin of 1). It caused a delay in post-natal development (safety margin of 1).<br>Pitolisant/metabolites were shown to cross the placenta barrier in animals. | |
| Interaction with drugs displaying histamine H1 receptor antagonism activity. | SmPC §4.5:<br>Antidepressants<br>Tri or tetracyclic antidepressants (e.g. imipramine, clomipramine, mirtazapine) may impair the efficacy of pitolisant because they display histamine H1-receptor antagonist activity and possibly cancel the effect of endogenous histamine released in brain by the treatment.<br>Anti-histamines<br>Anti-histamines (H1-receptor antagonists) crossing the haemato-encephalic barrier (e.g. pheniramine maleate, chlorpheniramine, diphenydramine, promethazine, mepyramine) may impair the efficacy of pitolisant. | None proposed |
| QT-interval prolongation | SmPC section 4.4<br>In two dedicated QT studies, supra-therapeutic doses of pitolisant (3-6-times the therapeutic dose, that is 108 mg to 216 mg) produced mild to moderate prolongation of QTc interval (10-13 ms). In clinical trials, no specific cardiac safety signal was identified at therapeutic doses of pitolisant. Nevertheless, patients with cardiac disease, co-medicated with other QT-prolonging medicinal products or known to be at risk of repolarization disorders, or co-medicated with medicinal products that significantly increase pitolisant Cmax and AUC ratio (see section 4.5) or patients with severe renal or moderate hepatic impairment (see section 4.4) should be carefully monitored (see section 4.5).<br>SmPC section 4.5<br>QT-prolonging drugs or known to be at risk of repolarization disorders: Combination with pitolisant should be made with a careful monitoring (see section 4.4).<br>SmPC §5.3<br>Pitolisant blocked hERG channel with an IC50 exceeding therapeutic concentrations and induced QTc prolongation in dogs. | None proposed |
| CYP2D6 genetic polymorphism | SmPC section 5.2<br>The metabolisation of pitolisant in humans is not fully characterized. The available data show that the major non-conjugated metabolites are | None proposed |

| Safety concern | Routine risk minimisation measures | Additional risk minimisation measures |
|---|---|---|
| | hydroxylated derivatives in several positions. The 5-aminovaleric acid is the major phase I inactive metabolite and is found in urine and serum. It is formed under the action of CYP3A4 and CYP2D6.<br>Other routine risk minimisation measures<br>An open label, single-period repeated dose study designed to assess the mass balance recovery, metabolite profile and metabolite identification of [14C]-pitolisant, at steady-state conditions, in healthy CYP2D6 phenotyped subjects.<br>Objective and justification: To address regulatory agency questions regarding the absorption and elimination pathways and circulating metabolites of pitolisant after repeated doses in healthy volunteers and in poor CYP2D6 metabolizer subjects. | |

## Missing information

| Safety concern | Routine risk minimisation measures | Additional risk minimisation measures |
|---|---|---|
| Long-term safety | SmPC § 4.8<br>Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V | None proposed |
| Pharmacokinetic interactions | SmPC §4.4<br>The combination of pitolisant with drugs substrates of CYP3A4 and having a narrow therapeutic margin should be avoided.<br>SmPC §4.5<br>Drugs affecting pitolisant metabolism<br>Enzyme inducer<br>Co-administration of pitolisant with rifampicin in multiple dose significantly decreases pitolisant mean $C_{max}$ and AUC ratio about 39% and 50%, respectively. Therefore, co-administration of pitolisant with potent CYP3A4 inducers (e.g. rifampicin, phenobarbital, carbamazepine, phenytoin) should be done with caution. With St John's Wort (Hypericum Perforatum), due to its strong CYP3A4 inducing effect, caution should be exercised when taken concurrently with pitolisant. A clinical monitoring should be made when both active substances are combined and, eventually a dosage adjustment during the combination and one week after the inducer treatment.<br><br>CYP2D6 inhibitors<br>Co-administration of pitolisant with paroxetine significantly increases pitolisant mean $C_{max}$ and $AUC_{0-72h}$ ratio about 47% and 105%, respectively. Given the 2-fold increase of pitolisant exposure, its coadministration with CYP2D6 inhibitors (e.g. paroxetine, fluoxetine, venlafaxine, duloxetine, bupropion, quinidine, terbinafine, cinacalcet) should be done with caution. A dosage adjustment during the combination could eventually be considered.<br><br>Drugs that pitolisant may affect metabolism<br>CYP3A4 and CYP2B6 substrates<br>Based on in vitro data, pitolisant and its main metabolites may induce CYP3A4 and CYP2B6 at | None proposed |

| Safety concern | Routine risk minimisation measures | Additional risk minimisation measures |
|---|---|---|
| | therapeutic concentrations. No clinical data on the magnitude of this interaction are available.<br>Therefore, the combination of pitolisant with drugs substrates of CYP3A4 and having a narrow therapeutic margin (e.g. immunosuppressants, docetaxel, kinase inhibitors, cisapride, pimozide, halofantrine) should be avoided. With other CYP3A4 substrates and CYP2B6 substrates (e.g. efavirenz, bupropion) caution should be made with a clinical monitoring of their efficacy.<br>With oral contraceptives, the combination with pitolisant should be avoided and a further reliable contraceptive method used.<br><br>Substrate of OCT1<br>.Pitolisant shows greater than 50% inhibition towards OCT1 (organic cation transporters 1) at 1.33 µM, the extrapolated $IC_{50}$ of pitolisant is 0.795 µM.<br>Even if the clinical relevance of this effect is not established, caution is advised when pitolisant is administered with a substrate of OCT1 (e.g. metformin (biguanides)) (see section 5.2)<br><br>SmPC section 5.2<br>The available data show that the major non-conjugated metabolites are hydroxylated derivatives in several positions. The 5-aminovaleric acid is the major phase I inactive metabolite and is found in urine and serum. It is formed under the action of CYP3A4 and CYP2D6.<br>On liver microsomes, pitolisant does not significantly inhibit the activities of the cytochromes CYP1A2, CYP2C9, CYP2C19, CYP2C8, CYP2B6, CYP2E1 or CYP3A4 and of uridine diphosphate glucuronosyl transferases isoforms UGT1A1, UGT1A4, UGT1A6, UGT1A9 and UGT2B7 up to the concentration of 13.3µM, a level considerably higher than the levels achieved with therapeutic dose. Pitolisant is an inhibitor of CYP2D6 with moderate potency ($IC_{50}$ = 2.6 µM).<br>Pitolisant induces CYP3A4, CYP1A2 and CYP2B6 *in vitro*. Clinically relevant interaction are expected with but only with CYP3A4 and CYP2B6 susbtrates and by extrapolation, UGTs, CYP2C and P-gp susbtrates.<br>Pitolisant does not induce uridine diphosphate glucuronosyltransferases isoforms:, UGT1A1, UGT1A4, UGT1A6, UGT1A9 and UGT2B7 at therapeutic concentrations. In vitro studies indicate | |

| Safety concern | Routine risk minimisation measures | Additional risk minimisation measures |
|---|---|---|
| | that pitolisant is neither a substrate nor an inhibitor of human P-glycoprotein and breast cancer resistance protein (BCRP). Pitolisant is not a substrate of OATP1B1, OATP1B3. Pitolisant is not a significant inhibitor of OAT1, OAT3, OCT2, OATP1B1, OATP1B3, MATE1, or MATE2K at the tested concentration. Pitolisant shows greater than 50% inhibition towards OCT1 (organic cation transporters 1) at 1.33 µM, the extrapolated IC50 of pitolisant is 0.795 µM (see section 4.5). | |
| Paediatric patients | SmPC § 4.2<br>The safety and efficacy of pitolisant in children aged from 0 to 18 years old have not yet been established. No data are available.<br>SmPC § 4.5<br>Interaction studies have only been performed in adults | None proposed |
| Patients with underlying severe cardiovascular disease, | SmPC §4.4<br>In two dedicated QT studies, supra-therapeutic doses of pitolisant (3-6-times the therapeutic dose, that is 108 mg to 216 mg) produced only mild to moderate prolongation of QTc interval (10-13 ms). In clinical trials, no specific cardiac safety signal was identified at therapeutic doses of pitolisant. Nevertheless, patients with cardiac disease, co-medicated with other QT-prolonging medicinal products or known to be at risk of repolarization disorders, or co-medicated with medicinal products that significantly increase pitolisant Cmax and AUC ratio (see section 4.5) or patients with severe renal or moderate hepatic impairment (see section 4.4) should be carefully monitored (see section 4.5). | None proposed |
| Patients with severe depression and anxiety | SmPC §4.4<br>Pitolisant should be administered with caution in patients with history of psychiatric disorders such as severe anxiety or severe depression with suicidal risk ideation risk. | None proposed |
| Patients with severe hepatic impairment (Child Pugh C) | SmPC §4.3<br>Contraindication for Severe hepatic impairment (Child-Pugh C). | None proposed |
| Patients with renal impaired renal function (creatinine clearance <15 ml/min) | SmPC § 4.2<br>In patients with renal impairment, the maximum daily dose should be 18 mg.<br>SmPC §4.4 | None proposed |

| Safety concern | Routine risk minimisation measures | Additional risk minimisation measures |
|---|---|---|
| | Pitolisant should be administered with caution in patients with renal impairment and dosing regimen should be adapted according to section 4.2.<br>SmPC § 5.2<br>Limited data are available in elderly. Therefore, dosing should be adjusted according to their renal hepatic status (see section 4.2 and 4.4).<br>In patients with impaired renal function (stages 2 to 4 according to the international classification of chronic kidney disease, i.e. creatinine clearance between 15 and 89 ml/min), $C_{max}$ and AUC tended to be increased by a factor of 2.5 without any impact on half-life (see section 4.2). | |

## *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.

## *2.9. Product information*

### 2.9.1. 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.*

### 2.9.2. Labelling exemptions

A request of translation exemption of the labelling as per Art.63.1 of Directive 2001/83/EC has been submitted by the applicant and has been found unacceptable by the QRD Group.

The majority of the Member States affected by the proposal for English only labelling (outer carton and bottle labels) were of the opinion that first option should be the creation of multilingual packs; an attempt should be made to accommodate as many languages as feasible from a readability point of view.

Certain countries would already accept English only labelling, therefore, there was still the option for the applicant to contact Member States individually in line with art. 63.3 to request a translation exemption on the basis of severe problems of availability.

### 2.9.3. Additional monitoring

Pursuant to Article 23(1) of Regulation No (EU) 726/2004, Wakix (pitolisant) is included in the additional monitoring list as it contains new active substance.

Therefore the summary of product characteristics and the package leaflet includes a statement that this medicinal product is subject to additional monitoring and that this will allow quick identification of new safety information. The statement is preceded by an inverted equilateral black triangle.

# 3. Benefit-Risk Balance

***Benefits***

**Beneficial effects**

The efficacy on excessive daytime sleepiness was measured on subjective (ESS) and objective (MWT) endpoints. The statistically significant improvement on ESS was shown against placebo in Harmony I study (-3.0 points; 95%IC [-5.6; -0.4]; p=0.024) and in Harmony CTP (3.41 [-4.95; -1.87]; p<0.0001). The effect was also shown on MWT in Harmony I, Ibis and CTP. In Harmony I, no significant difference in comparison to modafinil (first line treatment in narcolepsy) was observed.

The responder rate on ESS was also used as secondary endpoint. For both responders definitions (DEF1 = normalisation of the symptom; DEF2 = normalisation or clinically significant improvement) pitolisant showed significant results in both pivotal studies and in the supportive CTP study.

The effect on cataplexy was observed in the first pivotal study (Harmony I) and the supportive study (Harmony CTP) conducted in patients with high cataplexy frequency. The daily cataplexy rate in Harmony I improved against placebo with a rate ratio rR=0.38 whilst in the Harmony CTP the ratio of improvement on weekly cataplexy rate against placebo was 0.512.

The results of quality-of-life measurements showed an improvement in patients treated by pitolisant compared to placebo group, even though the difference was not statistically significant.

**Uncertainty in the knowledge about the beneficial effects**

Results of primary endpoints analysis in the Harmony Ibis study were not statistically significant. In this study, pitolisant was also significantly inferior on ESS final score when compared to modafinil in post-hoc sensitivity analysis. The upper dose of 20 mg/d of pitolisant used in this study, even though efficacious in almost 1/3 of patients in Harmony I, seems to have been insufficient in the remaining patients. This conclusion was supported by the results from cataplexy rate analysis: pitolisant at 20 mg/d did not show positive effect compared to placebo, which was not consistent with the results on cataplexy from Harmony I.

However, the results of the supportive Harmony CTP study provided supportive evidence as to pitolisant's efficacy, especially with regards to the effect on cataplexy. Accordingly, they were included in SmPC section 5.1.

The 8-week duration of the pivotal trials was considered sufficient to demonstrate efficacy. Long-term efficacy data were collected from an extension open-label study and compassionate use program and suggest the maintenance of effect. However, no formal withdrawal or controlled long term efficacy study was performed. The information regarding maintenance of effect has been included in section

5.1 of the SmPC and the physicians have been advised that the continued efficacy of treatment should be regularly evaluated.

No evidence on the effect of pitolisant on disease course is available. Pitolisant does not reverse the loss of orexin neurones, but instead acts by circumventing this and activating the neurones downstream from the damaged ones. In that respect, the treatment is purely symptomatic.

***Risks***

**Unfavourable effects**

No major safety concern was identified in clinical trials conducted in heterogeneous adult populations (291 healthy volunteers, 1094 patients including 342 patients in the treatment of narcolepsy and 752 in other indications). Cumulative duration of exposure to pitolisant was 1 year and above in 219 patients, between 6 months to 1 year in 150 and less than 6 months in 725 subjects (335 patients treated 1 month or less).

Pitolisant was associated with neuropsychiatric adverse events, which was expected as the histamine H3R receptors are almost exclusively expressed in the central nervous system. The most frequently reported neuropsychiatric AEs were headache (8%), insomnia (6%), depression (2%), anxiety (1.57%), dizziness (1.6%), irritability (1%), vertigo (1%) and malaise (0.5%). Gastro-intestinal AEs, in particular nausea (4%), vomiting (1%) and diarrhoea (1%) were also frequently observed.

There was apparently a dose-dependent relationship between the daily dose used of pitolisant and the incidence of overall AEs (10.4% at 5 mg/d; 20.6% at 10 mg/d; 32.9% at 20 mg/d; 36.1% at 40 mg/d). Therefore, the titration of the dose is recommended when initiating the treatment with pitolisant and the dose can be decreased if needed, depending on individual patient's response.

**Uncertainty in the knowledge about the unfavourable effects**

Pitolisant acts as an agonist to sigma-1 and antagonist to sigma-2 with very low Ki. Therefore, an effect on depression and abuse potential is theoretically plausible in humans. These risks could not be excluded by currently available non-clinical and clinical data. Consequently, relevant information and warnings have been included in the SmPC. It has been also stated that pitolisant should be prescribed by a physician experienced in the treatment of sleep disorders.

Based on non-clinical and clinical pharmacology results, fertility disorders, exposure during pregnancy and/or lactation, pro-convulsive potential and cardiac toxicity (QT prolongation) were considered as potential risks and will be closely monitored post-approval via routine pharmacovigilance activities. Appropriate warnings have been included in the SmPC.

There are still some gaps in the understanding of the pharmacokinetics of the drug. Therefore, the Applicant has been requested to conduct as post-approval measures a number of PK studies in order to further elucidate the contribution of different enzyme pathways to pitolisant's metabolism and characterise the risk of drug-drug interactions.

No clear pattern on weight change could be determined from available clinical data, as weight increase (2.7% in narcolepsy studies), but also to a lesser extent weight decrease, have been observed in patients treated with pitolisant. The excess body mass index and obesity are co-morbidities frequently encountered in narcolepsy. However, the potential effect of pitolisant on weight and appetite is unclear. A warning has been included in section 4.4 and in case of significant weight change treatment should be re-evaluated by the physician.

Uncertainties remain on long-term effects, in particular on cognition, depression and ulcer formation. Given the relatively low number of patients exposed to pitolisant longer than 6 months, long term safety has been considered as missing information in the RMP and will be further characterised through a Post Authorisation Safety Study, in addition to routine pharmacovigilance activities.

Pitolisant was not investigated in paediatric population, pregnant and/or breast feeding women, population with severe renal or hepatic impairment or with any other significant abnormality in the physical examination or clinical laboratory results. Thus, these populations were also considered as missing information in the RMP and will be closely monitored via routine pharmacovigilance activities.

### *Benefit-risk balance*

#### Importance of favourable and unfavourable effects

The results of the short-term studies support an effect of pitolisant in the treatment of narcolepsy with or without cataplexy. The minimal difference of 3 points on final ESS score between pitolisant and placebo groups pre-defined in clinical trials and exceeded in Harmony I and Harmony CTP studies is considered to be clinically relevant. The cataplexy rate (weekly in Harmony CTP and daily in Harmony I) was reduced significantly compared to placebo after 5 to 6 weeks of stable dose treatment.

Based on available data, the safety profile of pitolisant is acceptable in the treatment of narcolepsy with or without cataplexy. No major safety concern was identified in the clinical trials and adverse events can be often managed by individual dose adaptation.

#### Benefit-risk balance

The CHMP considers that the benefit-risk balance of pitolisant is positive.

### *Discussion on the benefit-risk balance*

Narcolepsy is an orphan debilitating disease, with limited therapeutic options. Pitolisant is a first-in-class drug acting on histamine H3 receptors mainly present in the brain. Its mechanism of action is different from the currently available treatments: CNS psychostimulants (i.e. modafinil) or CNS depressant (sodium oxybate) so it can offer an alternative option for the patients and physicians.

Efficacy of pitolisant has been demonstrated on both major clinical symptoms of narcolepsy; excessive daytime sleepiness and cataplexy. Therefore, the approved indication is the treatment of narcolepsy with or without cataplexy.

As pitolisant is intended to be administered chronically, the benefit-risk balance in the long term treatment will be further characterised by a Post Authorisation Safety Study.

## Effects Table

| Effect | Short description | Unit | Pitolisant compared to Placebo | Pitolisant compared to Modafinil | Uncertainties / Strength of evidence |
|---|---|---|---|---|---|
| **Favourable effects**<br>**Short-term studies (Harmony I, Ibis and CTP)** | | | | | |
| **ESS** | Mean geometric change vs baseline | Unit points | H1: -3.3 [-5.83; -0.83]; p<0.05<br><br>H1bis: -1.94 [-4.05; -0.07]; p=0.065<br><br>HCTP: -3.41 [-4.95; -1.87]; p<0.0001 | H1: 0.12 [-2.5; 2.7]<br><br>H1bis: -2.75 [-4.48; -1.02]<br><br>Not measured | Validated EDS subjective endpoint (primary in H1 and secondary in HCTP). Statistically and clinically significant effects in H1 and HCTP, non clinically relevant in H1bis. The hypothesis of non-inferiority of pitolisant compared to modafinil was rejected according to a margin of non inferiority of 2 in H1 and H1bis (no active comparator in HCTP study).<br><br>Long term efficacy data are issued from an open label (12-month treatment) and companionate use program, but no withdrawal/maintenance of efficacy study conducted in this indication. |
| **ESS responders (DEF1)** | Final ESS score≤10 (abnormal values≥11) | % | H1: 45.2% vs 13.3% (p<0.001)<br><br>H1bis: 30.3% vs 21.9% (p=0.017)<br><br>HCTP: 39.2% vs 18.0% (p=0,035) | H1: 45.2% vs 45.5% (p=0.894)<br><br>Analysis not performed<br><br>Not included | For both responders definitions (DEF1 = normalisation of the symptom; DEF2 = normalisation or clinically significant improvement) Wakix showed significant results in both pivotal studies and in the supportive CTP study. |
| **ESS responders (DEF2)** | ESSF≤10 or ESSF-ESSBL≥3 | % | H1: 71.0% vs 43.3% (p=0.010)<br><br>H1bis: 66.7% vs 43.8% (p=0.02)<br><br>HCTP: 68.6% vs 34.0% (p=0.002) | Analysis not performed<br><br>Analysis not performed<br><br>Not included | |
| **MWT**<br><br>**H1**<br>**H1bis**<br>**HCTP** | Mean geometric change vs baseline | Unit points<br>Ratios | ~+ 2 min compared to placebo<br><br>OR: 1.47 [1.01 ; 2.14]; p=0.044<br>OR: 1.57 [1.12; 2.20]; p=0.009<br>OR: 1.8 [1.2 ; 2.7]; p=0.005 | <br><br>OR: 0.77 [0.52 ; 1.13]; p=0.173<br>OR: 1.05 [0.80; 1.38]; p=0.713<br>Not included | Validated EDS objective endpoint.<br>Statistically and clinically significant effects. |

| | | | | | |
|---|---|---|---|---|---|
| **Cataplexy rate*** | Mean geometric change vs baseline | Ratio | H1: 0.38 [0.16; 0.93]; p=0.034<br><br>H1bis: NS<br><br>HCTP: 0.512 [0.435; 0.603]; p<0.0001 | H1: 0.70 [0.23; 1.63]; p=0.396<br><br>H1bis: NS<br><br>Not included | The effect of Wakix on cataplexy is observed by the significant reduction of cataplexy rate (daily and weekly rate in H1 and HCTP, respectively) compared to placebo after 5 to 6 weeks of stable dose treatment. While in Harmony I and CTP studies, the effect of Wakix on cataplexy was demonstrated, in Harmony Ibis this effect is unclear. |

| Effect | Short description | Unit | Pitolisant | Placebo | Modafinil | Uncertainties / Strength of evidence |
|---|---|---|---|---|---|---|
| **Unfavourable effects** | | | | | | |
| **Headache**<br>**Irritability**<br>**Dizziness**<br>**Vertigo** | Incidence in pooled clinical trials | % of total events | 8%<br>1.4%<br>1.6%<br>1% | 9.1%<br>0.4%<br>1.8%<br>0.4% | 12.3%<br>2.3%<br>5.8%<br>0% | Most of these common AEs were dose-dependent and could be manageable notably by individual dose adaptation. |
| **Insomnia** | Incidence in pooled narcolepsy clinical trials | % of total events | 6% | 3.3% | 0% | Insomnia was one of the most frequently reported adverse event in pitolisant treated patients and was the most frequently reported term associated with treatment cessation in clinical trials. This identified risk could be managed by taking the dose in the morning and dose reduction. |
| **Gastric disorders** | Incidence in pooled clinical trials | % of total events | 3.5% | 1% | 0% | Uncertainty remains on long-term effects related to gastric acidity (i.e. ulcer). |
| **Anxiety**<br>**Depression** | Incidence in pooled narcolepsy clinical trials | % of total events | 1.7%<br>1.9% | 0.7%<br>0.2% | 2%<br>0.7% | Uncertainty remains on these risks as psychiatric AEs represent frequent comorbidities in narcolepsy that make analysis of causal relationship difficult. |
| **Weight increase** | Incidence in pooled narcolepsy clinical trials | % of total events | 0.8% | 0.4% | 0% | Weight increase appears to be dose-dependent. |

Abbreviations: H1 = Harmony I study; H1bis = Harmony Ibis; HCTP = Harmony CTP; ESSB = baseline value of ESS; ESSF = final value of ESS; EDS excessive daytime sleepiness; NS=non significant

Notes: * daily cataplexy rate in Harmony I and Ibis studies and weekly cataplexy rate in Harmony CTP study.

# 4. Recommendations

***Outcome***

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the risk-benefit balance of Wakix in the treatment of narcolepsy with or without cataplexy is favourable and 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 (See Annex I: Summary of Product Characteristics, section 4.2).

***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.

The marketing authorisation holder shall submit the first periodic safety update report for this product within 6 months following authorisation.

***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 complete post-authorisation measures**

The MAH shall complete, within the stated timeframe, the below measures:

| Description | Due date |
|---|---|
| Non-interventional post-authorisation safety study (PASS):<br>A multi-center, observational post-authorization safety study to document the drug utilisation of Wakix and to collect information on the safety of Wakix when used in routine medical practice | Final report: 3Q 2023 |

***New Active Substance Status***

Based on the CHMP review of data on the quality properties of the active substance, the CHMP

considers that pitolisant hydrochloride is qualified as a new active substance.