26 January 2023
EMA/CHMP/180217/2023
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Wakix

International non-proprietary name: pitolisant

Procedure No. EMEA/H/C/002616/II/0030

Note

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

Official address Domenico Scarlattilaan 6 ● 1083 HS Amsterdam ● The Netherlands
Address for visits and deliveries Refer to www.ema.europa.eu/how-to-find-us
Send us a question Go to www.ema.europa.eu/contact **Telephone** +31 (0)88 781 6000 An agency of the European Union

Table of contents

List of abbreviations

Abbreviation	Definition
ADR	adverse drug reaction
AE	adverse event
AESI	adverse events of special interest
ANCOVA	analysis of covariance
AUC	area under the concentration-time curve
β-HCG	beta human chorionic gonadotrophin
BDRMs	blinded data review meetings
BMI	body mass index
CASS	Child and Adolescent Sleepiness Scale
CDI	Childhood Depression Inventory
CGI	Clinical Global Impression
CGI-C	Clinical Global Impression of Change
CGI-S	Clinical Global Impression of
CI	confidence interval
CNS	central nervous system
COVID-19	Coronavirus Disease 2019
CP	Conditional Power
CRF	case report form
CSR	clinical study report
C-SSRS	Columbia-Suicide Severity Rating Scale
DB2	Final double-blind last 2 weeks
DB4	Final double-blind last 6 weeks
DBP	diastolic blood pressure
Di	date of interruption
DSMB	Data Safety Monitoring Board
DSM IV	Diagnostic and Statistical Manual of Mental Disorders, fourth version
DT	dual task
EC	Ethics Committee
ECG(s)	electrocardiogram(s)
eCRF	electronic case report form
EDS	excessive daytime sleepiness
ESS	Epworth Sleepiness Scale
EudraCT	European Union Drug Regulating Authorities Clinical Trials Database
FAS	Full Analysis Set
FDA	Food and Drug Administration
HR	heart rate
ICF	informed consent form
ICSD-3	International Classification of Sleep Disorders Third Edition
IEC	Independent Ethics Committee
IWRS	Interactive Web Response Services
J2R	jump to reference
LMM	linear mixed model
LS	least squares
MAR	missing at random
Max	maximum
MCMC	Markov chain Monte Carlo
MedDRA	Medical Dictionary for Regulatory Activities
Min	minimum
MNAR	missing not at random
MI	multiple imputation
MSLT	Multiple Sleep Latency Test
MWT	maintenance of wakefulness test
NHS	number of hallucinations and sleep paralysis episodes
Night D	night duration
NSAE	number of diurnal involuntary sleep attacks and episodes of severe daytime sleepiness
OR	odd's ratio

PDSS	Pediatric Daytime Sleepiness Scale
PDSSB	Pediatric Daytime Sleepiness Scale at baseline
PDSSF	Pediatric Daytime Sleepiness Scale final value
PGO	patient's global opinion
PGO-C	patient's global opinion of change, defined as patient having improved (when PGO=3, 2 or 1) and considered as responder to therapy
PIS	patient information sheet
PK	pharmacokinetic
PP	Per Protocol
PPS	Per Protocol Set
PT	Preferred Term
Q1	quartile 1
Q3	quartile 3
QtcD	Qtc delta
QTcF	Fridericia's corrected QTc interval
EM	rapid eye movement
rR	rate Ratio
RS	Randomized Set
SAE	serious adverse event
SAP	statistical analysis plan
SBP	systolic blood pressure
SD	standard deviation
SE	standard error
SEM	standard error of the mean
SNRI(s)	serotonin and norepinephrine reuptake inhibitor(s)
SOC	System Organ Class
SP	paradoxical sleep
SSRI(s)	selective serotonin reuptake inhibitor(s)
TEA-Ch	Test of Everyday Attention for Children
TEAE(s)	treatment-emergent adverse event(s)
UNS	Ullanlinna Narcolepsy Scale
UNS-CTP	Ullanlinna Narcolepsy Scale-cataplexy
UNS-EDS	Ullanlinna Narcolepsy Scale-excessive daytime sleepiness
WHO-DDE	World Health Organization Drug Dictionary Enhanced
WMA	World Medical Association
WRC	weekly rate of cataplexy

1. Background information on the procedure

1.1. Type II variation

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, Bioprojet Pharma submitted to the European Medicines Agency on 6 April 2022 an application for a variation.

The following variation was requested:

Variation requested		**Type**	**Annexes affected**
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I and IIIB

Extension of indication to include treatment of narcolepsy with or without cataplexy in adolescents and children from the age of 6 years, based on results from Study P11-06; an ongoing phase III, double-blind, multicentre, randomized, placebo-controlled trial undertaken to evaluate safety and efficacy of pitolisant in children from 6 to less than 18 years with narcolepsy with/without cataplexy. As a consequence, sections 4.1, 4.2, 4.4, 4.8, 5.1 and 5.2 of the SmPC are updated. The Package Leaflet is updated in accordance.
Version 7.0 of the RMP has also been submitted.

Information relating to orphan designation

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

Information on paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included an EMA Decision P/0057/2021 on the agreement of a paediatric investigation plan (PIP) and the granting of a product-specific waiver.

At the time of submission of the application, the PIP P/0057/2021 was completed. The PDCO issued an opinion on compliance for the PIP P/0057/2021.

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 MAH 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.

Protocol assistance

The MAH did not seek Protocol Assistance at the CHMP.

1.2. Steps taken for the assessment of the product

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

Rapporteur: Jean-Michel Race Co-Rapporteur: N/A

Timetable	Actual dates
Submission date	6 April 2022
Start of procedure:	18 June 2022
CHMP Rapporteur Assessment Report	12 August 2022
PRAC Rapporteur Assessment Report	19 August 2022
PRAC members comments	24 August 2022
Updated PRAC Rapporteur Assessment Report	25 August 2022
PRAC Outcome	1 September 2022
CHMP members comments	5 September 2022
Updated CHMP Rapporteur(s) (Joint) Assessment Report	9 September 2022
Request for supplementary information (RSI)	15 September 2022
CHMP Rapporteur Assessment Report	23 December 2022
PRAC Rapporteur Assessment Report	2 January 2023
PRAC members comments	n/a
Updated PRAC Rapporteur Assessment Report	n/a
PRAC Outcome	12 January 2023
CHMP members comments	19 January 2023
Updated CHMP Rapporteur Assessment Report	19 January 2023
CHMP opinion:	26 January 2023

2. Scientific discussion

2.1. Introduction

2.1.1. Problem statement

Disease or condition

Narcolepsy is a rare, chronic neurological disorder, known as an "orphan disease", frequently occurring from childhood and persisting through adolescence and adulthood. Individuals suffering from narcolepsy exhibit excessive daytime somnolence, sleep attacks, cataplexy and dyssomnia where nocturnal sleep is usually fragmented and may be associated with sleep paralysis and hypnagogic hallucinations.

Claimed therapeutic indication

Wakix is indicated in adults, ***adolescents and children from the age of 6 years*** for the treatment of narcolepsy with or without cataplexy (see also section 5.1).

Epidemiology

The prevalence of narcolepsy in childhood is not known but can be estimated from adult studies to be greater than 20-60 per 100,000 (0.02% to 0.06%) in Western countries. [Longstreth, 2007; Lecendreux et al. 2013; Partinen, 2014].

Initial symptoms of narcolepsy occur before the age of 18 in over 50% of patients and may start at a very young age also before puberty onset, often with stronger symptoms than in adults [Bassetti et al. 2021]. On average, the prevalence is reported to be approximately 0.025-0.05%, and in at least half the cases the disease starts in childhood and adolescence [Plazzi et al. 2018].

Most studies assessing the prevalence of narcolepsy are questionnaire-based or interview- based, without a formal diagnosis being known, therefore the prevalence estimates could reflect a mixture of subtypes 1 and 2. In addition, the long diagnostic delay (8–12 years from disease onset) could cause an underestimation of the prevalence. However, in recent years, probably owing to increasing disease awareness, more cases have been diagnosed sooner after onset, especially in children.

Although the onset of narcolepsy can occur at any age (ranging from 3 to 80 years), in most patients, disease onset is in adolescence or early adulthood [Ohayon et al. 2005]. The onset of symptoms tends to be bimodal: the highest peak is around 15 years of age, and a smaller peak around 36 years of age [Dauvilliers et al. 2001, Thorpy et al. 2014]. In fact, it was shown in one study that more than one third of narcoleptic patients experienced the first symptoms of their disease before the age of 15 years [Challamel et al. 1994], which is particularly invalidating at the age of learning.

Paediatric narcolepsy is also associated with comorbidities including rapid weight gain, precocious puberty, and ADHD, and increased risk for deficits in social functioning, depression, and anxiety. School performance is also typically impaired, requiring special education services [Plazzi et al. 2018]. A recently published systematic review of the literature showed that more than 30% of children with narcolepsy presented symptoms of ADHD [Kim et al. 2020].

Biologic features

Narcolepsy with or without cataplexy can be secondary to brain tumors or several rare diseases, but in most cases it is a primary condition, better explained by the selective loss of hypocretin neurons in the posterolateral hypothalamus. [Lecendreux et al. 2014]

Clinical presentation, diagnosis

The presentation of narcolepsy can be very variable, making the diagnosis difficult. Narcolepsy is a long-term sleep disorder which affects the brain's ability to regulate the normal sleep-wake cycle. This leads to symptoms such as an irresistible urge to sleep, even at inappropriate times and places, and disturbed night-time sleep. Some patients also have episodes of severe muscle weakness (cataplexy) that can cause collapse. Narcolepsy occurs during childhood in combination with cataplexy in two-thirds of patients. Symptoms may develop rapidly over a few weeks or months, with excessive daytime sleepiness (EDS) and cataplexy being the most dramatic and observable symptoms.

The diagnosis criteria have been defined in the revised International Classification of Sleep Disorders (ICSD- 3, AASM 2014) and separate the narcolepsy with cataplexy (Type 1) and the narcolepsy without cataplexy (Type 2) as presented in Table 1.

Table 1: Narcolepsy according to the International Clasification of Sleep Disorders (ICSD—3)

Type 1 = Narcolepsy with cataplexy	*Type2 =Narcolepsy without cataplexy*
A. **Excessive Daytime Sleepiness** (EDS) occurring almost daily for at least 3 months	
B. **History of cataplexy**, defined as sudden and transient episodes of loss of muscle tone triggered by emotions, is present	B. **Typical cataplexy is not present**, although doubtful or atypical cataplexy-like episodes may be reported
C.1 Diagnosis confirmed by nocturnal polysomnography followed by an MSLT Mean sleep latency on the **MSLT ≤ 8 min**, And **2 or more SOREMPs** (sleep-onset rapid eye movement periods) observed following sufficient nocturnal sleep (minimum 6 h) during the night prior to the test. A SOREMP (within 15 min of sleep onset) on the preceding nocturnal PSG may replace one SOREMPs on the MSLT.	
C.2 Alternatively, **hypocretin-1 levels** in the cerebrospinal fluid (CSF) are **less than or equal to 110 pg/mL**, or one-third of mean normal control values.	
D. **Diurnal hypersomnia not better explained** by another sleep disorder, medical or neurological disorder, mental disorder, medication use, or substance use disorder	

The onset of type 1 narcolepsy (NT1) usually begins when the patient is from 10 to 20 years old, while narcolepsy type 2 (NT2) seems to be less frequent compared with NT1 [Franceschini et al. 2020].

Management

According to guidelines published by the European task force [Billiard et al. 2006, Bassetti et al. 2021], management of narcolepsy with or without cataplexy relies on several classes of drugs, namely stimulants for EDS, antidepressants for cataplexy, and hypno-sedative drugs for disturbed nocturnal

sleep [Dauvilliers et al. 2003]. However, the use of these treatments may be limited by associated adverse effects and because the dosing regimen may require a nocturnal intake.

Treatment options for children with narcolepsy are largely managed by sleep specialists and involve management of alertness and sleep. Off-label medications for alertness include stimulants (amphetamine and non-amphetamine), and wake-promoting agents such as modafinil, and the histamine receptor antagonists – pitolisant [Inocente et al. 2012, Lecendreux et al. 2020].

Cataplexy may be managed with serotonin reuptake inhibitors (fluoxetine), tricyclic antidepressants (clomipramine), or selective norepinephrine reuptake inhibitors (venlafaxine) [Franceschini et al. 2020]. Cataplexy, daytime sleepiness, and night-time sleep quality can be managed with sodium oxybate in paediatrics > 7 years of age. Some drugs, like sodium oxybate, have high potential for abuse and require careful oversight [Thorpy et al. 2020]. Pitolisant showed absence or low abuse potential according to clinical data (Setnik, 2020).

According to the current European guidelines for treatment for EDS in narcolepsy in paediatrics [Bassetti et al. 2021], sodium oxybate (authorised in the EU and US), or methylphenidate, modafinil, pitolisant and amphetamine derivates are recommended as first line monotherapy treatment. Combination therapies including pitolisant are recommended for EDS with cataplexy, associated or not with disturbed nocturnal sleep.

In addition to symptoms, narcolepsy has often a negative impact on the child's psychological well-being, and non-pharmacological treatment, such as cognitive behavioural therapy, or counselling, may also be necessary.

2.1.2. About the product

WAKIX was authorised by the European Medicines Agency (EMA) in 2016 and is indicated in adults for the treatment of narcolepsy with or without cataplexy.

Pitolisant is a potent, orally active histamine H3-receptor antagonist/inverse agonist which, via its blockade of histamine auto-receptors enhances the activity of brain histaminergic neurons, a major arousal system with widespread projections to the whole brain.

Pitolisant also modulates various neurotransmitter systems, increasing acetylcholine, noradrenaline and dopamine release in the brain. However no increase in dopamine release in the striatal complex including nucleus accumbens was evidenced for pitolisant. Pitolisant has been developed in adult patients with narcolepsy with or without cataplexy through Phase II and Phase III clinical studies, with an overall good tolerance and favourable efficacy results. Pitolisant significantly reduced the diurnal somnolence compared to placebo, confirming its wakening effect against EDS on the ESS and demonstrating its anti-cataplectic effect when administrated on an individual titration scheme established on basis of individual benefit/tolerance ratio.

2.1.3. The development programme/compliance with CHMP guidance/scientific advice

The MAH did not seek Protocol assistance at the CHMP.

A Paediatric Investigation Plan (PIP) for pitolisant was submitted in 2012 and granted for paediatric age subsets 6 to less than 18 years, and with a waiver granted in 0 to less than 6 years based on the grounds that the disease practically does not occur in this paediatric age subset.

Recently, in May 2022, the compliance was checked and considered fulfilled, once some requests

regarding the Statistical Analysis Plan and change of the primary endpoint have been solved.

2.2. Non-clinical aspects

No new clinical data have been submitted in this application, which was considered acceptable by the CHMP.

2.3. Clinical aspects

2.3.1. Introduction

GCP

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

2.3.2. Pharmacokinetics

A pharmacokinetic study (P11-11, single oral dose of 20 mg pitolisant) in patients with narcolepsy aged 6 to less than 18 years was conducted as a prerequisite for the paediatric trial P11-06 and has already been submitted and assessed in 2017 (variation EMEA/H/C/002616/II/0007). The study was also recently published by Lecendreux and colleagues [Lecendreux et al. 2020] and the conclusion was "After single-dose administration, the exposure parameters of pitolisant were significantly greater in the younger paediatric patients (aged 6 to<12 years) compared with older paediatric patients (aged 12 to<18 years) with narcolepsy. Compared with adults, pitolisant exposure was approximately twofold higher in the older paediatric group and approximately threefold higher in the younger paediatric group, which was partially explained by differences in body weight. Titration of pitolisant to 17.8 mg/d was considered appropriate for younger children (body weight<40 kg), and dose increases up to a maximum of 35.6 mg/d for older adolescents who are approaching the adult range of body weight".

The analysis of clinical information relevant to dosing recommendations for children and adolescents 6-18 years is based on the results of the pharmacokinetics study (P11-11) and information already presented for Wakix and authorised in adults (not exceeding the dose of 40 mg/d). Overall, for the same weight, pitolisant exposure was roughly comparable, regardless of the age, suggesting that body weight was of more influence on PK variation than age. Therefore, in order to not overexpose paediatric patients with a body weight below 40 kg, the maximum daily dose of pitolisant was limited to 20 mg for those patients.

2.3.3. Pharmacodynamics

No new information on pharmacodynamics are provided which is acceptable.

2.3.4. Discussion on clinical pharmacology

The aim of study P11-11 study was to specify the PK parameters of pitolisant administered on a single oral dose of 20 mg in patients from 6 to less than 18 years. For the same weight pitolisant exposure was roughly comparable, regardless of the age, suggesting that body weight was of more influence on PK

variation than age. Thus, it seemed reasonable, in order to not overexpose paediatric patients with a body weight below 40 kg, to limit the maximum daily dose of pitolisant to 20 mg. For paediatric patients with a body weight > 40 kg, the recommended posology scheme as displayed for adults in the SmPC is applicable. This single oral daily dose is in accordance with the PK conclusion of variation EMEA/H/C/002616/II/0007.

2.3.5. Conclusions on clinical pharmacology

The pharmacology aspect of this application are addressed sufficiently.

2.4. Clinical efficacy

2.4.1. Main study

Title of Study: P11-06 Study

Double-blind, multicentre, randomized, placebo-controlled trial to evaluate safety and efficacy of pitolisant in children from 6 to less than 18 years with narcolepsy with/without cataplexy, followed by a prolonged open-label period.

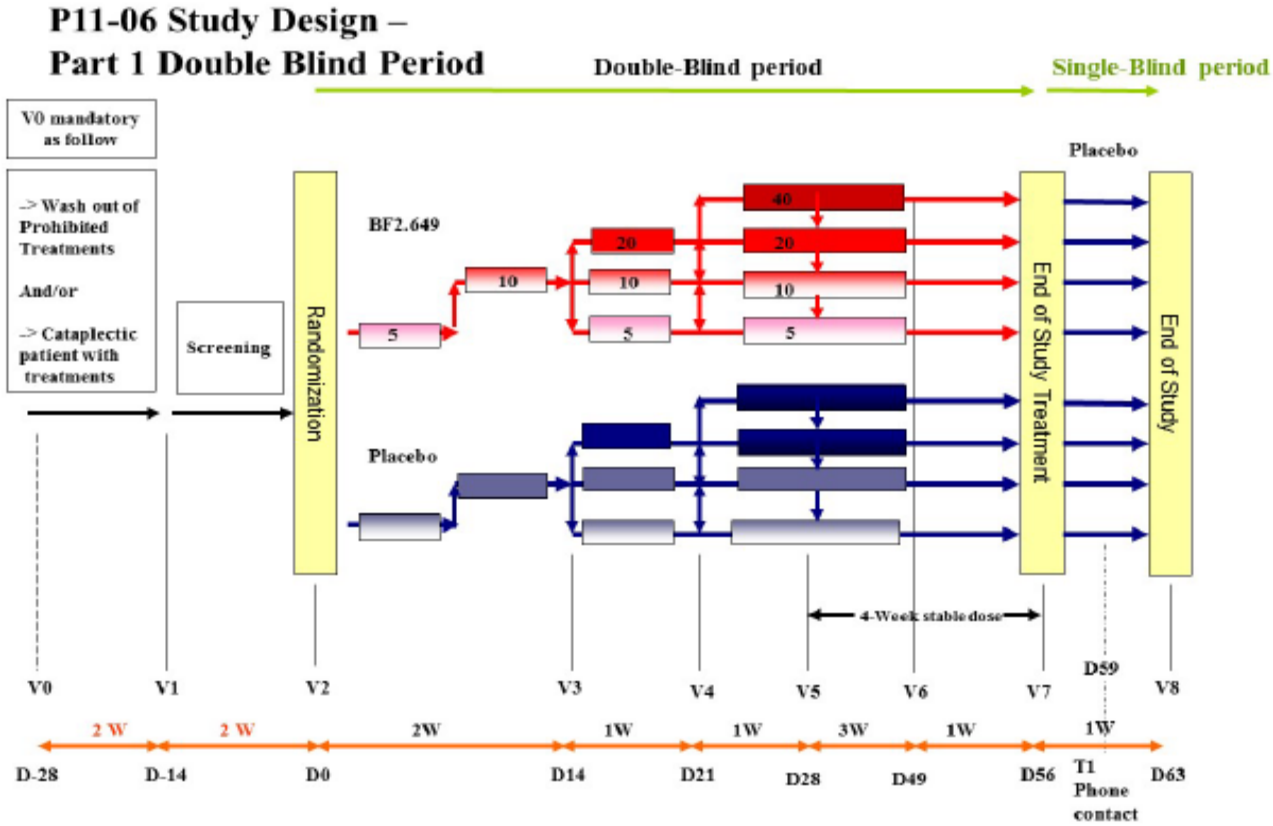
Methods

This is a double-blind, multicentre, randomized, placebo-controlled study to evaluate the safety and efficacy of pitolisant in children aged from 6 to less than 18 years with narcolepsy with or without cataplexy meeting the International Classification of Sleep Disorders Third Edition (ICSD-3) criteria (narcolepsy type 1 and type 2).

The study was planned to include 108 patients, more or less (at least 40%) equally balanced between age groups (6 to 11 years and 12 to17 years) and sex.

A schematic of the study design for the double-blind period is presented in Figure 1:

Figure 1: Study Design – Part 1 Double-Blind Period



The study comprised a 28-day screening period that included a 2-week baseline period, an 8-week double blind period (treatment with pitolisant or placebo, from V2 [D0] to V7 [D56]), a 1-week single blind washout period (placebo treatment, from V7 [D56] to V8 [D63]), and a currently ongoing prolonged open-label period with pitolisant treatment for patients willing to continue in the study.

There were 3 protocol amendments, with amendment 1 applicable only in France and amendments 2 and 3 applicable in all participating countries:

- Protocol Version 1.01 (France) dated 01 February 2016,
- Protocol Version 2.0 (all countries) dated 19 June 2018,
- Protocol Version 3.0 (all countries) dated 30 September 2020.

The main changes were summarized in Table 2:

Table 2: Protocol Amendments

Protocol Amendment (date)	Main Changes
First amendment – France (01 Feb 2016)	• Clarification of inclusion criteria #1: polysomnography only had to be performed if not already performed within the last 12 months; • At V2 and V7, an optional polysomnography could be done.
Second amendment – All countries (19 Jun 2018)	• Increase of the sample size, 96 patients; • Inclusion of intermediary doses from V10; a Note to File dated 03 April 2017 recorded a substantial amendment in France at the request of Professor Dauvilliers in order to optimize the effectiveness and tolerability of treatment; two intermediate doses (15 mg and 30 mg) were included from V10 during the open-label period of the study ; • Clarification on dose adjustment at T2; • Correction of Section 4.1.2 – removal of recommendations on tablets to be taken depending on the patient age (global protocol only, this was previously updated in Protocol Version 1.0 France dated 07 December 2015); • Addition of new analysis once 40 patients were included; • Addition of Appendix 4 Childhood Depression Inventory.
Third amendment – All countries (30 Sep 2020)	• Increase of the sample size, 108 patients; • Change of the primary endpoint to UNS instead of PDSS and update of the main secondary endpoint accordingly (see Section 9.2); • Update of the statistical analysis sections; • Inclusion of the recommendation on the phone visits during the COVID-19 pandemic; • Update of storage conditions.

Abbreviations: COVID-19=Coronavirus Disease 2019; PDSS=Pediatric Daytime Sleepiness Scale; T2=telephone contact at D91 (±1 day); UNS=Ullanlinna Narcolepsy Scale; V=visit.

The main issue was the change of the primary endpoint scale to UNS instead of PDSS and update of the main secondary endpoints accepted within the framework of the third amendment. Their justification is described in the endpoint criteria section below.

For the duration of the COVID-19 pandemic, some special measures were introduced to limit the risk for the patient to spread/acquire the infection (Protocol Amendment 3 dated 30 September 2020):

• Study site visits could be replaced by telephone visits. During these calls, the investigator assessed the efficacy and tolerance and adjusted the dose of treatment accordingly, when relevant;

• Direct shipment of study treatment from the site, or hospital pharmacy, to the patient's home. Patients returned all medication at their subsequent site visit. Diaries to be documented daily were sent to the patient with the study treatment.

An independent DSMB followed the progress of the clinical study and monitored safety data.

Study participants

The main inclusion criteria for this study were as follows:

1. Male and female children from 6 to less than 18 years of age (at V8) suffering from narcolepsy with or without cataplexy – meeting the ICSD-3 criteria (narcolepsy type 1 and type 2). The diagnosis is confirmed with polysomnography and Multiple Sleep Latency Test MSLT for patients without cataplexy if these examinations had not been performed within the last 12 months.

2. PDSS score ≥ 15 during baseline period (V1+V2)/2.

3. Patients free of non-authorized medication, in particular psychostimulant treatments as from the screening visit (V0) onwards.

4. Use of an efficient birth control method, throughout the study and during the month following treatment discontinuation, for pubescent female.

The main specific non-inclusion criteria are as follows:

1. Any other conditions that could have been considered the primary causes of EDS (sleep related breathing disorders, chronic sleep deprivation, circadian sleep wake rhythm disorder, or any other medical or neurological causes);

- Treatment by anticataplectics, if not stable since at least 4 weeks at the time of inclusion

- Treatment by tricyclic antidepressants (clomipramine, imipramine …) because they display histamine H1 receptor antagonist activity. They can possibly interfere with the effect of pitolisant by abrogating the effect of endogenous histamine released in brain by pitolisant.

- Any significant abnormality of the ECG and particularly QTcF (QTcF=QT/3$\sqrt{}$ 60/HR) higher than 450 ms.

The inclusion and non-inclusion criteria are appropriate for the aim of the study.

Patients were allowed to continue their anti-cataplectic drugs (including sodium oxybate) if they were at a stable dosage for at least 4 weeks before the inclusion visit (V2) and maintained at a stable dosage throughout the study (from V2 to V8). The previous use of drugs with a psychotropic effect, including psychostimulants for the treatment of EDS (amphetamine and amphetamine-like CNS stimulants, methylphenidate, or others such as modafinil) or medication with sedating properties (e.g., benzodiazepines, non-benzodiazepine anxiolytics, hypnotics sedatives, neuroleptics, opioids, antihistaminic products (1st generation), and anticonvulsants) should have been discontinued at V0 (D-28).

Treatments

Following the completion of inclusion procedures, patients were randomized to treatment with pitolisant or placebo in a 2:1 ratio. Study treatment was to be taken orally every day in the morning before breakfast.

The total treatment duration of the double-blind period was 8 weeks. Patients started pitolisant or placebo treatment with escalating doses scheme on the first 4 weeks. The dosage regimen during the 8-week double-blind period is described below.

- Week 1: Pitolisant at 5 mg/day (1 tablet of pitolisant 5 mg) or placebo for 7 days.
- Week 2: Pitolisant at 10 mg/day (2 tablets of pitolisant 5 mg) or placebo for 7 days.
- Week 3: The dose could be increased to 20 mg/day, or maintained at the same level i.e. 10 mg/day, or reduced to 5 mg/day, depending on investigator's assessment of efficacy and tolerability or placebo for 7 days.
- Week 4: The dose could be increased to up to 40 mg/day, or maintained at the same level i.e. 20 mg/day, or reduced to 10 or 5 mg/day, depending on investigator's assessment of efficacy and tolerability or placebo for 7 days:

*T*he dosing scheme with a weekly uptitration is in accordance with the SmPC currently recommendations for adults. Treatment dosage at 40 mg/day was not allowed for patients with a weight of <40 kg. Indeed,

for these patients, the maximum allowed dosage is 20 mg/day (in agreement with PK data as assessed in 2017 from study P11-11).

The use of a placebo group in this study was justified to obtain reliable scientific evidence for the evaluation of pitolisant in this pediatric population. Given the small population size and the rarity of the disease, the choice of this study design (2:1 ratio for pitolisant or placebo) was deemed appropriate, to ensure minimal exposure to placebo for a vulnerable population.

Objectives

Primary objective

The primary objective of this study is to compare pitolisant to placebo, with regard to EDS on the one hand, and to the number of cataplexy episodes, if any, on the other hand.

This study is characterizing the efficacy of pitolisant (5-, 10-, 20-, 40 mg/day in the double-blind period and 5-, 10-, 15-, 20-, 30-, 40 mg/day in the open-label period) compared to placebo in showing an incremental improvement to the situation particularly in terms of a reduction of EDS as measured by the Ullanlinna Narcolepsy Scale (UNS), and also on the number of cataplexy episodes, if any.

Secondary objectives

The secondary objectives of this study are to assess, between groups:

- *Changes in EDS measured:*
  - *By the Maintenance of Wakefulness Test (MWT);*
  - *By the Pediatric Daytime Sleepiness Scale (PDSS);*
  - *By the Child and Adolescent Sleepiness Scale (CASS);*
- *Changes in number of cataplexy episodes per weeks, recorded in sleep diary by patient and/or parent/teacher;*
- *Severity of EDS and cataplexy measured by the Clinical Global Impression of Severity (CGI-S) and Clinical Global Impression of Change (CGI-C);*
- *Differences in weekly frequency of cataplexy episodes, recorded in sleep diary by patient and/or parent/teacher;*
- *Changes in the Test of Everyday Attention for Children (TEA-Ch) test;*
- *Comparison in withdrawal symptoms questionnaire;*
- *Comparison in patient's global opinion (PGO) on treatment effect at the end of treatment;*
- *Clinical and biological tolerance of pitolisant.*

The secondary objectives (changes in EDS, changes in number of cataplexy episodes per weeks, severity of EDS and cataplexy, differences in weekly frequency of cataplexy episodes, changes in the Test of Everyday Attention for Children and comparison in patient's global opinion) are relevant objectives in accordance with the requested assessments for this kind of condition in support to the primary objective.

The comparison in withdrawal symptoms and the clinical and biological tolerance of pitolisant are further assessed in the safety part of this AR.

Outcomes/endpoints

Primary endpoint

The primary efficacy endpoint was the changes in UNS measuring the intensity and frequency of symptoms of narcolepsy (EDS and cataplexies), based on the change from baseline (mean of two pre-treatment measures at [(V1 + V2)/2]) of the UNS score and at the end of double-blind period (mean of the last two measures [(V6 + V7)/2]).

- The UNS is an 11-item scale used to measure the intensity and frequency of symptoms of narcolepsy (EDS and cataplexy) which was validated in 1994 by Hublin et al with high level of sensitivity and of specificity therefore considered as an accurate scale for assessment of the symptoms of the narcoleptic syndrome. The first 4 items address typical manifestations of cataplexy occurring when laughing, becoming glad or angry, or in an exciting situation. The 7 other items measure the sleep latency and the propensity to fall asleep in various situations.

The response to treatment according to UNS was categorized as follows:

• The cataplexy score (UNS-CTP): Sum of the first 4 items (knees unlocking symptoms, mouth opening symptoms, head nodding symptoms, and falling down symptoms);

• The EDS score (UNS-EDS): Sum of the other 7 items (fall asleep during reading, fall asleep during travelling, fall asleep during standing, fall asleep during eating, fall asleep during other unusual, fast to fall asleep the evening, and sleep during the day).

The total score varies from 0 to 44, with higher scores denoting greater narcoleptic tendencies. The UNS was evaluated at V1 and V2 (i.e., prior to randomization) as baseline evaluation and at V6 and V7 (i.e., end of the double-blind period).

A responder was defined by a score reduction of at least 3 points between the PDSS at baseline and the PDSS final value.

The primary efficacy endpoint was initially planned to be the PDSS, which evaluates EDS. The protocol was later amended (third protocol amendment) to use the UNS as the primary efficacy endpoint. The rationale for this change was that the UNS demonstrates better reliability, does not vary with unspecific conditions (demographic variables), and has higher sensitivity to change compared with the PDSS. In addition, the UNS evaluates both therapeutic targets i.e., the major narcolepsy symptoms of EDS and cataplexy.

Secondary endpoints

The following secondary efficacy endpoints in pitolisant and placebo groups were assessed in the Part 1 Double-Blind Period of the study:

• Changes in EDS measured by the PDSS between baseline ([V1 score (D-14) + V2 score (D0)]/2) and the end of treatment ([V6 score (D49) + V7 score (D56)]/2);

• Changes in Ullanlinna Narcolepsy Scale-cataplexy (UNS-CTP) between baseline ([V1 score (D-14) + V2 score (D0)]/2) and the end of treatment ([V6 score (D49) + V7 score (D56)]/2). This subscore is defined as the sum of the first 4 items of the UNS;

• Changes in the average number of cataplexy episodes per weeks (weekly rate of cataplexy [WRC]) (recorded in sleep diary by patient and/or parent/teacher) between the 2 weeks of baseline (V1, V2) and the 2 weeks of end study treatment period (V6, V7);

• Differences in weekly frequency of cataplexy episodes (recorded in sleep diary by patient and/or parent/teacher) between baseline and the 4 weeks of stable treatment period (V5 to V7);

• Changes in EDS as measured by the Maintenance of Wakefulness Test (MWT) between baseline (V2) and V7.

- The PDSS (Pediatric Daytime Sleepiness Scale) is a sum score with 8 items leading to a score range of 0 to 32. A score >13 is considered as abnormal sleepiness. This scale has been validated in 2003 by Drake et al. (The Pediatric Daytime Sleepiness Scale (PDSS): Sleep habits and school outcomes in middle-school children. Sleep 2003).

The PDSS is a simple instrument constituted by 8 items: "How often do you fall asleep or get drowsy during class periods"; "How often do you get sleepy or drowsy while doing your homework"; "Are you usually alert most of the day"; "How often are you ever tired and grumpy during the day"...

Each of the 8 questions is rated from 0=never, 1=seldom, 2=sometimes, 3=often, frequently to 4=very often, always. The total score ranges between 0 and 32 with higher scores representing greater sleepiness. A score >13 is considered as abnormal sleepiness.

The PDSS was evaluated at each study visit from V1 to V8, or at the early withdrawal visit and reviewed by the investigator. The PDSS should have been administrated to the patient at approximately the same time of the visit day and with same delay after the investigational treatment intake in order to standardize the possible impact of the treatment on the evaluation.

The patient should have been helped in the comprehension of the questionnaire until he/she fully understood the 8 questions of the score. The patient was to be reminded that the PDSS measures the subjective sleepiness with regard to the immediate past week.

- The cataplexy score (UNS-CTP): see above, a component of the primary endpoint focused on cataplexy.

- The WRC (Weekly Rate of Cataplexy) is the weekly frequency of cataplexy episodes, recorded in sleep diary by patient and/or parent/teacher whose differences are measured at different steps, either at the end of treatment compared to baseline or during the 4 weeks of stable treatment period compared to baseline.

- The MWT was used in this study to assess an individual's ability to remain awake while resisting the pressure to fall asleep. Patients were administrated four 30-minute MWT sessions at 2-hour intervals at the inclusion visit (V2) and at the endpoint visit (V7 or the last on-study visit), according to validated standard (Doghramji et al. 1997 where the MWT appears to be a useful procedure in differentiating groups with normal daytime wake tendency from those with impaired wake tendency).

Sample size

The initial protocol was based in assuming a Pearson correlation coefficient of R=0.5 between pre-baseline and final values of PDSS, two pre-baseline measurements [(V1+V2)/2] and two post-baseline measurements [(V6+ V7)/2]. A standardized mean difference of at least 0.5 (considered as the minimum clinically significant difference) would have been detected at a two-sided 0.05 confidence level with a power of at least 0.8, when the sample size/group was at least 20 and 40 patients for control and tested drug groups, respectively.

The sample size was based on the value of the assumed standardize mean difference and the correlation between baseline and final values (R). Over- or under-estimation or R was possible. An estimation of R would be found, blind to treatment, when at least 20 patients had completed the study producing an 80% half interval length of R. In case where the difference between the observed R' values and the expected R was such that |R-R'|>1 the sample size was to be recalculated and discussed with the DSMB. Initially, at least 60 patients were required to evaluate the primary endpoints (40 patients being

administered pitolisant, and 20 patients receiving placebo). Besides, the analysis of sample size justified in the context of an adaptive sample size was performed on 29 enrolled patients including 27 randomized patients and among them 25 patients provided endpoints values at V6 and V7. The statistical outcomes highlighted the need for increase of the sample size. At least 96 patients (64 patients being administrated pitolisant, and 32 patients receiving placebo) were needed for a power of at least 0.75, given the observed values of standard deviation (SD) and baseline correlation.

At a later stage, UNS measuring EDS and cataplexy was used as the primary outcome instead of the PDSS. As UNS was expected with a residual variability larger than PDSS, the initial power of 0.75 was judged as too small, and a recalculation of the sample size was performed on a standardized mean difference of 0.5 on the UNS (considered as the minimum clinically significant difference), a ratio 1:2, and a correlation R=0.4. Under these assumptions, and analysis of covariance (ANCOVA) test at 0.05 two-sided confidence level, the probability of a significant effect would be found with a power of 0.85 when the sample size exceeded 36+72 patients for control and tested drug groups, respectively, thus a total of 108 patients.

The sample size was planned to show with 85% power and a 5% 2-sided type 1 error rate, a standardized mean difference of 0.5 (effect size) based on the UNS score, with a ratio of 1:2 and a correlation coefficient of 0.4, which is considered acceptable.

Sample size calculation is based on the standardized mean difference which is not easily interpretable from a pure clinical point of view.

Randomisation

During the double-blind period patients were randomized to treatment with pitolisant or placebo in a 2:1 ratio according to a pre-defined randomization list. Randomization and double-blinding were used to minimize bias in treatment allocation and in the assessment of safety and efficacy, and minimize bias arising from the expectations of the investigators, individuals who collected the study data, and patients and/or their parent(s)/guardian(s). Randomization was stratified by study centre. There was no pre-allocation of randomization blocks to a specific centre. Allocation of randomization blocks was made automatically by the system during randomization.

Blinding (masking)

The patient, investigator, and other study personnel remained blinded regarding the treatment assigned to the patients throughout the 8-week double-blind period.

Packaging and treatment boxes were identical in appearance in pitolisant and placebo groups.

In the situation where the knowledge of the treatment appeared imperative and urgent, a procedure to open the code for the individual patient existed. A set of sealed envelopes, identified by the study number, contained the type of treatment assigned to the corresponding patient. These envelopes must have only been opened in cases where there was an imperative need to know the assigned treatment to protect the patient's health and well-being, such as voluntary or involuntary overdosing. The code break was to be documented on the envelope and in the patient's eCRF, with date and time and reasons of disclosure and signed by the investigator. All envelopes were to be tracked by the Sponsor at the completion of the study.

Statistical methods

Analysis Sets and Subgroups:

• Screened Set: all patients with an ICF signed;

• Randomized Set (RS): all randomized patients;

• Full Analysis Set (FAS): in accordance with the ITT principle and Section 5.2.1 of the ICH E9 guideline, all randomized patients who received at least one dose of study treatment and who had at least one baseline value of UNS (primary efficacy criterion)

• Per Protocol Set (PPS): all patients in the FAS without any major protocol deviation and having one total score UNS value at V6 or V7. A protocol deviation was major when it had a possible effect on the outcome. As to whether a deviation was major or minor was agreed during the Blind Review Meeting. The Per Protocol (PP) analysis was conducted at the condition that its sample size should be less than 90% of the FAS.

• Safety Set: all patients who received at least one treatment dose.

All efficacy analyses were performed by randomized treatment group in the FAS and PPS. All safety analyses were performed by actual treatment group in the Safety Set. There were no interim analyses planned for this study.

The following four subgroups were used in some analyses:

• Age at baseline ([6-11], [12-18[).

• Sex.

• Body mass index (BMI) at baseline (underweight, normal, overweight, and obese).

• Type of narcolepsy (type 1 or type 2).

Descriptive Statistics

Continuous variables were described using number of non-missing observations, number of missing observations, arithmetic mean, standard deviation (SD), minimum, quartile 1 (Q1), median, quartile 3 (Q3), and maximum. The 95% two-sided confidence interval (CI) was calculated when appropriate using the standard method (Standard normal distribution).

Categorical variables were presented using number of non-missing observations, number of missing observations, and percentages (%).

Pitolisant and placebo groups comparison – main inferential model: The significance of the difference between pitolisant compared with placebo was assessed through a general model of analysis of covariance (ANCOVA) in which the studied endpoint at final time (noted Yf) constituted the dependent variable of the model. Independent variables were (1) the baseline value of the studied endpoint (noted Yb) analyzed as a fixed covariate, (2) the treatment effect (Noted Trt) coded 0 (placebo) or 1 (pitolisant) (cell mean contrast formulation), and (3) the center considered as a random factor of the intercept constituted by a fixed part k0 and a random component N(0,σc).

This model is summarized by the following expression:

$Yif=(k0+\zeta) + kb\ Yb + kt\ Trt + \epsilon i$ $\epsilon i=N(0,\sigma$) and $\zeta=N(0,\sigma c)$ [general Model -1]

-This model does not assume a treatment-baseline interaction term (as required in EMA/CHMP/295050/2013). The decision of using center as a random factor is justified by the useless

estimate of each center, in focusing on the measurement of the SD of the intercept. The treatment was considered as fixed factor without center random component.

-This model is a linear mixed model (LMM) as it combines random and fixed factors, assumes linearity of baseline and hypothesizes the studied endpoint distributed according to a normal (Gaussian) distribution. This model constitutes the main model used in this study for all the studied endpoints unless otherwise specified.

Pitolisant and placebo groups comparison – multiple testing: The main analysis was defined as the ANCOVA following general Model 1 conducted on the main selection (FAS), on the primary endpoint (UNS) considered as a global endpoint aggregating both EDS and cataplexy symptoms. Secondary endpoints were PDSS and the UNS-CTP subscale measuring the pitolisant effect on EDS and cataplexy, respectively. Two other secondary endpoints were the WRC measured by the patient diary and the MWT. All the other endpoints were considered as exploratory and supportive.

The main endpoint (UNS) and the four secondary endpoints necessitated 5 tests. The fixed-sequence strategy was used testing the endpoints in the pre-defined order UNS, PDSS, UNS-CTP, WRC, and MWT, each one tested at two-sided alpha=0.05 significance, moving to the following endpoint conditionally to a significant difference reached on the previous endpoints (Food and Drug Administration. Multiple endpoints in clinical trials guidance for industry, 2017, section C.5). This strategy protected the results with type 1 risk bounded by p=0.05.

Missing data: Missing data were imputed for the five main endpoints of this study (UNS, PDSS, UNS-CTP, WRC, and MWT). For the other endpoints, no missing value was imputed. A multiple imputation (MI) procedure was used to impute the missing evaluations, as a prior step, assuming that those patients would be in their randomized arm.

Primary Efficacy Endpoint Methodology

The primary efficacy endpoint was defined as the change from baseline to final value in the total UNS raw score.

1-Primary Analysis

In order to meet the primary objective of the study, the superiority of pitolisant compared to placebo on efficacy after an 8-week treatment period was assessed, from the UNS total score expressed in terms of change from baseline to final value. After a MI, the main inferential model with the centre as random effect was used.

The primary estimand for the primary endpoint of the study is defined with mixed strategies for intercurrent events (based on the estimand terminology).

A summary of the main endpoint according to the Estimand Notation (ICH E9R1) is provided in Table 3.

Table 3: Primary Endpoint According to the Estimand Notation

Attribute	Primary Definition		Rationale (as needed)
Population	Intended to include narcoleptic children from 6 to less than 18 years of age with/without cataplexy		
Endpoint	UNS at V6, V7		
Intercurrent events	**Event**	**Strategy**	
	Receipt of assigned study treatment	Treatment policy	Strategy applied to align the estimand with the application of the intention-to-treat principle
	Prohibited concomitant medication during the study treatment period	While on treatment	Strategy applied to assess the treatment effect up to the last observation at or prior to the time of the prohibited concomitant medication, which marks the end of adherence to treatment
	Premature discontinuation from the study at any time	Hypothetical strategy	Strategy applied to estimate what the treatment effect would have been if patients adhered to the treatment by assuming that missing data arise from a MAR mechanism
Population summary	Difference in LS means from ANCOVA model between treatment groups		

Abbreviations: ANCOVA=analysis of covariance; LS=least squares; MAR=Missing at Random; UNS=Ullanlinna Narcolepsy Scale; V=visit.

2-Sensitivity and Other Analyses

Sensitivity analyses were performed to assess the robustness of the primary analysis results:

• Using MNAR option of the MI imputation (removing the treatment effect in the imputation model of the partially complete data sets);

• Using the same model as for the primary analysis, with the center as fixed factor effect instead of random effect;

• Using the same model as for the primary analysis, with in addition the oxybate sodium intake and treatment-by-oxybate sodium intake interaction as fixed effects;

• Using an observed cases analysis, the same model as for the primary analysis was performed in patients having a value of UNS total score at V6 or V7 (i.e., in this case analysis was restricted to completers of the double-blind period);

• Using the same model as for the primary analysis performed by actual treatment group, only if the actual group was different from the randomized group.

The same statistical elements to estimate the treatment effect as for primary analysis were provided.

Intermediate Analyses

A one–stage futility stopping was based on Conditional Power (CP), probability to detect a significant result at the end of the study, given the results observed at an intermediate time. CP was estimated through B-values [29, 30]. This analysis was originally planned when at least 20 patients were available, and futility threshold was Cpmin=.10 involving a slight increase of type 2 error (β=0.1/.9=.111-.10≅.01).

This analysis was delayed due to necessity of reconsideration of the sample size and a proposal of change of the main endpoint to be approved by the European Medicines Agency.

The futility analysis was performed through treatment-blind computerized calculation. The futility test did not detect a value of CP <0.05 and the conclusion was that the study may resume following the current conditions.

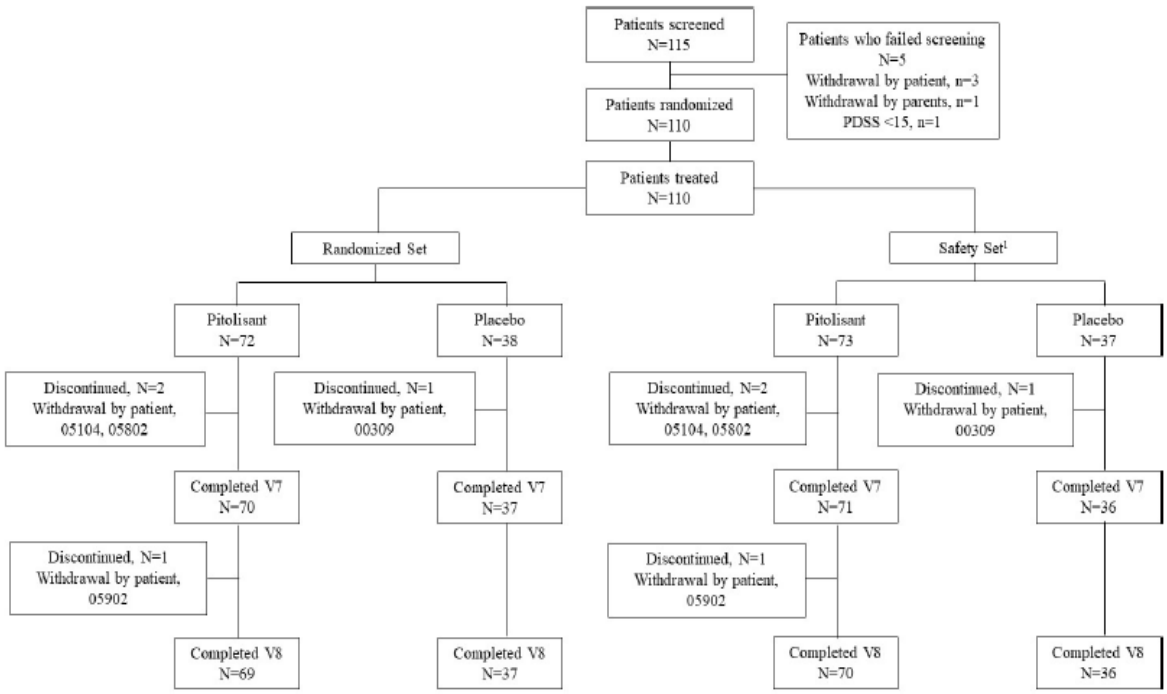
Overall, the statistical plan is considered acceptable. A linear mixed model was used to evaluate the UNS total score expressed in terms of change from baseline to final value after imputation of missing data. The center was included in the model as a random variable which is considered appropriate. However, there was a discrepancy in the planning and the reporting of the results of the intermediate futility analysis.

Results

Participant flow

Patients' disposition is presented in Figure 2 and Table 4 below:

Figure 2: Disposition of Patients in the Part 1 Double-Blind Period



Source: Table 14.1.1.2, Table 14.1.1.5, Table 14.1.1.7, Listing 16.2.4.2, Listing 16.2.6.1, Listing 16.2.10.1.
[1]Five (5) patients were provided the treatment kit without the correct randomization procedure (IWRS); 5 patients (5501, 5502, 5804, 5901, 5903) did not receive the correct planned treatmen
The randomization scheme not respected was reported as a major protocol deviation for these 5 patients (see Section 10.2).
Abbreviations: IWRS=Interactive Web Response Services; N=total number of patients; n=number of patients.

Table 4: Disposition of Patients in the Part 1 Double-Blind Period

Number of Patients	Pitolisant	Placebo	All
Screened patients, n			115
Randomized, n	72	38	110
Completed the double-blind period to V7			
Yes, n (%)	70 (97.2)	37 (97.4)	107 (97.3)
No, n (%)	2 (2.8)	1 (2.6)	3 (2.7)
Reason for discontinuation from the study			
Withdrawal by patient, n (%)	2 (100.0)	1 (100.0)	3 (100.0)
Completed the blinded period to V8			
Yes, n (%)	69 (95.8)	37 (97.4)	106 (96.4)
No, n (%)	3 (4.2)	1 (2.6)	4 (3.6)
Reason for discontinuation from the study			
Withdrawal by patient, n (%)	3 (100.0)	1 (100.0)	4 (100.0)

Source: Table 14.1.1.2, Table 14.1.1.5, Table 14.1.1.7.

Five (5) patients were provided the treatment kit without the correct randomization procedure (IWRS); 5 patients did not receive the correct planned treatment. The randomization scheme not respected was reported as a major protocol deviation for these 5 patients (see Section 10.2).

Abbreviations: IWRS=Interactive Web Response Services; n=number of patients.

A total of 110 patients were enrolled and randomized in the study: 72 patients in the pitolisant group and 38 patients in the placebo group.

107 patients (97.3%) completed Part 1 of the study to V7 (to the end of the 8-week double blind period), including a similar percentage of patients in the pitolisant group (97.2%) and the placebo group (97.4%). Three patients withdrew consent and discontinued from the study during this period (2 patients in the pitolisant group and 1 patient in the placebo group).

106 patients (96.4%) completed Part 1 of the study to V8 (to the end of the 1-week single blind washout), including a similar percentage of patients in the pitolisant group (95.8%) and the placebo group (97.4%). One patient in the pitolisant group withdrew consent and discontinued from the study during the 1-week single blind washout period.

The patients' disposition is well-balanced in both treatment groups. The sample size was increased twice through amendment 2 and 3 to get at least 108 patients assessed, which is reached with 110 patients enrolled and randomized.

Recruitment

Conduct of the study

This study was conducted in 11 centres (with screened patients) in 5 countries (France, 3 centres; Finland, 1 centre; Italy, 1 centre; Netherlands, 1 centre; Russia, 5 centres).

The first patient was included on 06 Jun 2016 and the last patient was included on 09 Jan 2021. The last patient completed the follow-up at V8 on 03 Apr 2021.

The efficacy results should not be affected by the change of the primary endpoint in the middle of the study for two main reasons:

1) The change was made when the blinding was maintained (the sponsor was not aware of efficacy results and of the differences between groups for each outcome)

2) The primary endpoint that was chosen lately (UNS) was already considered as a secondary endpoint in the first version of the protocol (p11-06-app1611 page 55) which means that it was recorded for the patients that were already enrolled in the trial.

According to the reflection paper on methodological issues in confirmatory clinical trials planned with an adaptive design (https://www.ema.europa.eu/en/documents/scientific-guideline/reflection-paper-methodological-issues-confirmatory-clinical-trials-planned-adaptive-design_en.pdf), as a general rule, changing a primary endpoint during the trial is not easy to accept (see ICHE9 statistical principles for clinical trials). However, in this trial, 2 criteria were considered to evaluate the efficacy of the treatment, UNS measuring EDS and cataplexy, and PDSS measuring EDS. Besides, the change of the order of these criteria was done in order to adapt to the evolution of the population, the majority of whom were with cataplexy. In addition, the trial was blinded and the endpoint that was primary is now key secondary. Therefore, in this case, nothing formally opposes the change even if not recommended and efficacy results could be considered reliable throughout the study.

Baseline data

- The demographic characteristics at inclusion in both treatments groups are displayed in Table 5:

Table 5: Demographic Characteristics at Inclusion (RS)

Characteristic	Pitolisant (N=72)	Placebo (N=38)	All (N=110)
Sex			
Female, n (%)	35 (48.6)	14 (36.8)	49 (44.5)
Male, n (%)	37 (51.4)	24 (63.2)	61 (55.5)
Age (years)			
Mean (SD)	13.0 (3.0)	12.5 (3.0)	12.9 (3.0)
Median	14	13	13
[Q1 ; Q3]	[11 ; 16]	[11 ; 15]	[11 ; 15]
[Min ; Max]	[6 ; 17]	[6 ; 17]	[6 ; 17]
Age in class (years)			
6-11 years old, n (%)	22 (30.6)	13 (34.2)	35 (31.8)
12-18 years old, n (%)	50 (69.4)	25 (65.8)	75 (68.2)
Body mass index (kg/m^2)			
Mean (SD)	23.8 (5.3)	23.3 (6.0)	23.6 (5.6)
Median	23	22	23
[Q1 ; Q3]	[21 ; 26]	[19 ; 28]	[20 ; 27]
[Min ; Max]	[15 ; 45]	[15 ; 41]	[15 ; 45]
Body mass index in category (kg/m^2)			
Normal, n (%)	30 (41.7)	18 (47.4)	48 (43.6)
Overweight, n (%)	19 (26.4)	7 (18.4)	26 (23.6)
Obese, n (%)	23 (31.9)	13 (34.2)	36 (32.7)

Source: Table 14.1.2.1, Table 14.1.2.2.

Abbreviations: max=maximum; min=minimum; N=total number of patients; n=number of patients; Q1=quartile 1; Q3=quartile 3; SD=standard deviation.

- More male than female patients (55.5% and 45.5%, respectively) were randomized in the study. This difference was also observed in the two treatment groups: in the pitolisant group, 51.4% of patients were male and 48.6% female and, in the placebo group, 63.2% of patients were male and 36.8% female.

According to the protocol, the study was planned to include 108 patients, more or less (at least 40%) equally balanced between age groups (6 to 11 years and 12 to 17 years) and sex. Unfortunately, in the placebo group, there were only 36.8% female. The MAH did not succeed in getting balance between male and female in the placebo group. However, the difference between the sex ratio is purely random because there is a satisfactory randomization; this difference may be the consequence of the small number of patients in the study (around 100 patients); it is clearly specified in the guideline "Guideline on adjustment for baseline covariates in clinical trials, 26 February 2015 EMA/CHMP/295050/2013 Committee for Medicinal Products for Human Use that "Statistical testing for baseline imbalance has no role in a trial where the handling of the randomization and blinding has been fully satisfactory". Therefore, only particular attention will be given to the effect of the treatment in each of the sex subgroups since the baseline data were not well-balanced.

- The mean (SD) and median (range) age of all patients was 12.9 (3.0) years and 13 (6 to 17) years, respectively, and was comparable for patients in the pitolisant group (13.0 [3.0] years) and placebo group (12.5 [3.0] years).

Regarding the age distribution, 35 patients (31.8%) were aged 6 to 11 years and 75 patients (68.2%) were aged 12 to 18 years. A comparable age group distribution (one third, two thirds) was observed in the two treatment groups: in the pitolisant group, 30.6% of patients were aged 6 to 11 years and 69.4% aged 12 to 18 years, and in the placebo group, 34.2% of patients were aged 6 to 11 years and 65.8% aged 12 to 18 years.

The proportion of males and females is displayed in Table 6. Patients aged <12 years were 62.9% male and 37.1% female and patients aged ≥12 years were 52.0% male and 48.0% female

Table 6: Gender by Age Group at Inclusion – Post-Hoc Analysis (FAS)

	Pitolisant	Placebo	All
Patients aged <12 years			
N	22	13	35
Female, n (%)	9 (40.9)	4 (30.8)	13 (37.1)
Male, n (%)	13 (59.1)	9 (69.2)	22 (62.9)
Patients aged ≥12 years			
N	50	25	75
Female, n (%)	26 (52.0)	10 (40.0)	36 (48.0)
Male, n (%)	24 (48.0)	15 (60.0)	39 (52.0)

Source: Table 14.4.4.5.1, Table 14.4.4.5.2.
Abbreviations: N=total number of patients; n=number of patients.

Contrary to what the MAH estimated, the CHMP considered that the gender distribution by age group is not well-balanced in both treatment groups since there are around 10% more female in patients aged ≥12 years or patients aged <12 years in the pitolisant group vs placebo group. The same reasoning is applied for male distribution, with around 10% less male in patients aged ≥12 years or patients aged <12 years in the pitolisant group vs placebo group. However, since the pathophysiology of narcolepsy is not different between male and female, this observation is not likely to have an influence on the efficacy results.

Otherwise 2/3 of patients were over 12 year of age.

- For body mass index (BMI), 48 patients (43.6%) were in normal class, 26 patients (23.6%) were in the overweight class, and 36 patients (32.7%) were in the obese class: in the pitolisant group, 41.7% of patients were in the BMI normal class, 26.4% were in the overweight class, and 31.9% were in the obese class and, in the placebo group, 47.4% of patients were in the BMI normal, 18.4% were in the overweight class, and 34.2% were in the obese class. Slightly (around 6%) more patients in the placebo group were in normal class whereas slightly (8%) more patients in the pitolisant group were in the overweight class.

If this BMI distribution would have an impact on efficacy results, a particular attention will be given to the effect of the treatment in each of the BMI subgroups.

- The mean (SD) DBP, SBP, and HR were comparable for patients in the pitolisant group and in the placebo group. The BP was interpreted as normal for the majority of patients (97.3% overall) and was interpreted as abnormal, not clinically significant for 3 patients (2.7%) who were all in the placebo group.

The majority of physical examination results were normal (i.e., without a significant clinical abnormality). Clinically significant abnormalities were reported in the following body systems: Neurological in 3 patients (2.7%), including 2 patients in the pitolisant group and 1 patient in the placebo group; Dermatologic in

2 patients (1.8%), including 2 patients in the pitolisant group; General status in 2 patients (1.8%), including 1 patient in the pitolisant group and 1 patient in the placebo group and Cardiovascular in 1 patient (0.9%), including 1 patient in the pitolisant group.

The interpretation of the ECG was normal for 77 patients (70.0%), including 53 patients (73.6%) in the pitolisant group and 24 patients (63.2%) in the placebo group. The ECG result was abnormal, non-clinically significant for 32 patients (29.1%), including 18 patients (25.0%) in the pitolisant group and 14 patients (36.8%) in the placebo group. The ECG could not be evaluated for 1 patient in the pitolisant group.

The fact that the QTCF class was ≤450 msec for all 110 patients (100.0%) is reassuring.

- The patient disease baseline characteristics (narcolepsy baseline disease severity and duration, UNS and PDSS scores) are displayed in Table 7:

Table 7: Narcolepsy Disease, UNS and PDSS Scores at Study Inclusion (RS)

	Pitolisant (N=72)	Placebo (N=38)	All (N=110)
Type of narcolepsy			
Type 1, n (%)	61 (84.7)	29 (76.3)	90 (81.8)
Type 2, n (%)	11 (15.3)	9 (23.7)	20 (18.2)
Narcolepsy duration since the confirmed diagnosis (years)			
Mean (SD)	1.5 (2.0)	1.8 (2.5)	1.6 (2.2)
Median	0	0	0
[Q1 ; Q3]	[0 ; 3]	[0 ; 3]	[0 ; 3]
[Min ; Max]	[0 ; 7]	[0 ; 9]	[0 ; 9]
Ullanlinna Narcolepsy Scale (UNS)– total score			
Mean (SD)	24.63 (7.80)	23.68 (9.08)	24.30 (8.23)
Median	25.0	24.5	24.8
[Q1 ; Q3]	[17.3 ; 31.0]	[16.0 ; 30.5]	[17.0 ; 31.0]
[Min ; Max]	[9.0 ; 39.5]	[3.5 ; 41.0]	[3.5 ; 41.0]
Paediatric Daytime Sleepiness Scale (PDSS)			
Mean (SD)	20.16 (3.64)	20.00 (3.49)	20.10 (3.57)
Median	19.8	19.3	19.5
[Q1 ; Q3]	[17.3 ; 22.5]	[17.0 ; 22.0]	[17.0 ; 22.5]
[Min ; Max]	[15.0 ; 31.5]	[15.5 ; 28.0]	[15.0 ; 31.5]

Source: Table 14.1.4.1, Table 14.1.5.1.
Abbreviations: max=maximum; min=minimum; N=total number of patients; n=number of patients; Q1=quartile 1; Q3=quartile 3; SD=standard deviation.

The baseline disease characteristics were overall comparable between the pitolisant and placebo groups.

The majority of patients (90 patients [81.8%]) had type 1 narcolepsy and 20 patients (18.2%) had type 2 narcolepsy. In the pitolisant group, 84.7% of patients had type 1 and 15.3% of patients had type 2 narcolepsy. In the placebo group, 76.3% of patients had type 1 and 23.7% of patients had type 2 narcolepsy.

The mean (SD) duration of narcolepsy since confirmed diagnosis for all patients was 1.6 (2.2) years (range, 0 to 9 years), and was 1.5 (2.0) years for patients in the pitolisant group and 1.8 (2.5) years for patients in the placebo group.

Consistent with a diagnosis of narcolepsy, the mean (SD) UNS total score for all patients was 24.30 (8.23), and it was 24.63 (7.80) for patients in the pitolisant group and 23.68 (9.08) for patients in the placebo group, considering a cut-off score of 14 for narcolepsy designation when using the UNS scale UNS was not an eligibility criteria but an assessment criteria.

Consistent with the study eligibility criteria, the PDSS score was ≥15, with a mean (SD) PDSS score of 20.10 (3.57) for all patients, and was 20.16 (3.64) for patients in the pitolisant group and 20.00 (3.49) for patients in the placebo group. The PDSS total score can range from 0 and 32 and a score >13 is considered abnormal sleepiness.

The narcolepsy-associated symptoms that were recorded at baseline included: hallucinations in 45 patients (40.9%); automatic behaviour in 39 patients (35.5%); dyssomnia in 68 patients (61.8%) and sleep paralysis in 29 patients (26.4%). Most of these narcolepsy-associated events were ongoing in around 80% of these patients.

- Prior treatment for narcolepsy

Overall, 38 patients (34.5%) reported previous treatments for narcolepsy. The percentage of patients reporting previous treatments for narcolepsy was slightly higher in the pitolisant group (36.1%) than the placebo group (31.6%).

The most frequently reported previous treatments for narcolepsy were centrally acting sympathomimetics reported by 26 patients (23.6%) overall, including 19 patients (26.4%) in the pitolisant group and 7 patients (18.4%) in the placebo group.

Since the percentage of patients reporting previous treatments for narcolepsy was slightly higher in the pitolisant group (36.1%) than the placebo group (31.6%), patients in the pitolisant group may be more severe and are mainly treated by centrally acting sympathomimetics. The previous treatment by sodium oxybate is similar between pitolisant (15.3%) and placebo group (15.8%).

Overall, 30 patients (27.3%) reported concomitant treatments during the treatment period (up to V8). This was comparable in the pitolisant group (26.4%) and the placebo group (28.9%).

The most frequently reported concomitant treatment for narcolepsy during the treatment period (reported by ≥10% of patients overall) was Sodium oxybate reported by 11 patients (10.0%) overall, including 9 patients (12.5%) in the pitolisant group and 2 patients (5.3%) in the placebo group.

Numbers analysed

A total of 115 patients were screened and 110 patients were enrolled and randomized. The analysis sets were as follows:

A total of 110 patients were randomized to receive pitolisant (72 patients) or placebo (38 patients) and received at least one dose of study treatment, and were therefore included in the RS (randomized set) and the FAS. The populations in the RS and FAS were identical.

Overall, 12 patients (10.9%) had at least 1 major protocol deviation during the study, with a lower proportion of patients in the pitolisant group (8.3% of patients) than the placebo group (15.8% of patients).

A total of 97 patients (88.2%) in the FAS did not have any major protocol deviations and had one total score UNS value at V6 or V7, and were therefore included in the PPS. The PPS included 65 patients (90.3%) in the pitolisant group and 32 patients (84.2%) in the placebo group.

The Safety Set included 73 patients in the pitolisant group and 37 patients in the placebo group. Five (5) patients were provided the treatment kit without the correct randomization procedure (IWRS); 5 patients did not receive the correct planned treatment.

Table 8: Summary of Analysis Sets

	Pitolisant	Placebo	All
Randomized Set[1], n (%)[5]	72	38	110 (95.7)
Full Analysis Set[2], n (%)[6]	72 (100.0)	38 (100.0)	110 (100.0)
Per Protocol Set[3], n (%)[7]	65 (90.3)	32 (84.2)	97 (88.2)
Safety Set[4], n (%)[5]	73	37	110 (95.7)

Source: Table 14.1.1.2.
[1]All randomized patients.
[2]All randomized patients who received at least one dose of study treatment and who had at least one baseline value of UNS (primary efficacy criterion).
[3]All patients in the FAS without any major protocol deviation and having one total score UNS value at V6 or V7.
[4]All patients who received at least one dose of study treatment.
[5]Percentages were calculated over the number of screened patients (N=115).
[6]Percentages were calculated over the number of randomized patients.
[7]Percentages were calculated over the number of FAS patients.
The randomization scheme was not respected for 5 patients.
The allocated treatment in the randomization list was taken for the patient without allocated treatment number.
Abbreviations: FAS=Full Analysis Set; N/n=number of patients; UNS=Ullanlinna Narcolepsy Scale; V=visit.

The randomized Set is similar to the FAS Set, to the PP Set and to the Safety Set. The number of withdrawals is rather low, which could partly be explained by the short duration of study.

Outcomes and estimation

- Extent of exposure

Treatment duration during the study is summarized by treatment group and for both groups in Table 9.

The median treatment duration was 56 days for all patients and for patients in the two treatment groups.

Table 9: Extent of Exposure of Pitolisant (FAS)

	Pitolisant (N=72)	Placebo (N=38)	All (N=110)
Treatment duration (days)			
Mean (SD)	55.6 (7.2)	57.0 (2.4)	56.1 (6.0)
Median	56	56	56
[Q1 ; Q3]	[56 ; 57]	[56 ; 57]	[56 ; 57]
[Min ; Max]	[6 ; 68]	[54 ; 64]	[6 ; 68]

Source: Table 14.1.8.4.
Abbreviations: max=maximum; min=minimum; N=number of patients; Q1=quartile 1; Q3=quartile 3; SD=standard deviation.

In this 8-week, randomized, double-blind study, patients started with escalating doses of pitolisant or placebo from 5 mg/day up to a maximum of 40 mg/day (for patients with a weight of ≥ 40 kg) for the

first 4 weeks, followed by treatment administration at a stable dose for 4 weeks and a 1-week placebo period. Study treatment was taken every day in the morning before breakfast, according to the Investigator's prescription regarding the dose regimen of patients, based on efficacy and tolerability.

Overall, during the treatment stable dose period, 1.4% of patients received 5 mg pitolisant, 15.5% received 10 mg pitolisant, 23.9% received 20 mg pitolisant, and 59.2% received 40 mg pitolisant.

The actual treatment intake in the pitolisant group during the stable dosing period according to age was as follows:

• **For patients aged <12 years**, 22.7% received 10 mg pitolisant, **45.5% received 20 mg pitolisant**, and 31.8% received 40 mg pitolisant during the stable dose period.

• **For patients aged ≥12 years**, 2.0% received 5 mg pitolisant, 12.2% received 10 mg pitolisant, 14.3% received 20 mg pitolisant, and **71.4% received 40 mg pitolisant** during the stable dose period.

The actual treatment intake in the pitolisant group during the stable dosing period according to weight was as follows:

• **For patients weighing <40 kg**, 30.8% received 10 mg pitolisant and **69.2% received 20 mg pitolisant** during the stable dose period. More than 30% of patients received a dose lower than the therapeutic dose.

• **For patients weighing ≥40 kg**, 1.7% received 5 mg pitolisant, 12.1% received 10 mg pitolisant, 13.8% received 20 mg pitolisant, and **72.4% received 40 mg pitolisant** during the stable dose period.

Table 10: Actual Treatment Intake During the Stable Dose Period According to Weight – Post-Hoc Analysis (Safety Set)

	Pitolisant Patients <40 kg (N=13)	Pitolisant Patients ≥40 kg (N=60)	Pitolisant Overall (N=73)
Stable dose			
N	13	58	71
Missing	0	2	2
5 mg, n (%)		1 (1.7)	1 (1.4)
10 mg, n (%)	4 (30.8)	7 (12.1)	11 (15.5)
20 mg, n (%)	9 (69.2)	8 (13.8)	17 (23.9)
40 mg, n (%)		42 (72.4)	42 (59.2)

Source: Table 14.4.5.3.1, Table 14.4.5.3.2, Table 14.4.7.1.
Abbreviations: N=total number of patients; n=number of patients.

Most patients received a daily dose of 20 mg (23.9%) or 40 mg (59.2%) whatever the age group. As recommended, no patient weighing <40 kg received a dose > 20 mg daily. For patients weighing ≥ 40 kg, the majority received a daily dose of 40 mg (72.4%).

- Primary endpoint: Change in mean UNS scores

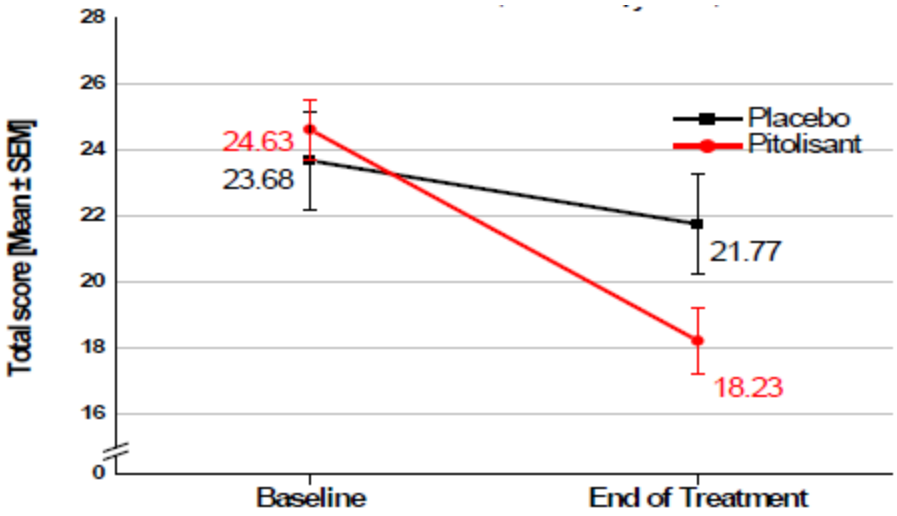
Table 11 presents mean changes from baseline to end of treatment (EoT) of UNS total scores for pitolisant and placebo, for the overall population and also by sex, age and BMI.

Table 11: Mean Change from Baseline to End of Treatment (EoT) Ullanlinna Narcolepsy Scale Total Severity Scores (FAS)

Treatment groups	Pitolisant			Placebo		
Overall population						
N (baseline/EoT)	72/70			38/37		
Baseline mean UNS total score (SD)	24.63 (7.80)			23.68 (9.08)		
EoT mean UNS total score (SD)	18.23 (8.14)			21.77 (9.25)		
Mean change from baseline (SD)	-6.36 (8.59)			-2.46 (5.55)		
By sex	***Males***	***Females***		***Males***	***Females***	
N (baseline/EoT)	37/35	35/35		24/23	14/14	
Baseline mean UNS total score (SD)	25.12 (7.50)	24.10 (8.18)		23.40 (9.50)	24.18 (8.63)	
EoT mean UNS total score (SD)	17.99 (7.97)	18.47 (8.42)		20.30 (8.40)	24.18 (10.37)	
Mean change from baseline (SD)	-7.09 (8.26)	-5.63 (8.97)		-3.96 (5.67)	0.00 (4.54)	
By age	***<12 years***	***≥12 years***		***<12 years***	***≥12 years***	
N (baseline/EoT)	22/22	50/48		13/13	25/24	
Baseline mean UNS total score (SD)	24.61 (7.68)	24.63 (7.93)		24.92 (8.55)	23.04 (9.44)	
EoT mean UNS total score (SD)	18.14 (9.16)	18.27 (7.73)		19.85 (8.04)	22.81 (9.84)	
Mean change from baseline (SD)	-6.48 (9.70)	-6.30 (8.14)		-5.08 (6.03)	-1.04 (4.83)	
By BMI	***Normal***	***Overweight***	***Obese***	***Normal***	***Overweight***	***Obese***
N (baseline/EoT)	30/29	19/19	23/22	18/18	7/7	13/12
Baseline mean UNS total score (SD)	22.47 (8.26)	24.55 (6.75)	27.50 (7.36)	22.61 (8.80)	27.00 (7.95)	23.38 (10.22)
EoT mean UNS total score (SD)	15.43 (8.64)	19.11 (6.95)	21.16 (7.50)	20.78 (9.90)	21.64 (10.96)	23.33 (7.65)
Mean change from baseline (SD)	-7.33 (9.45)	-5.45 (8.42)	-5.86 (7.78)	-1.83 (5.09)	-5.36 (7.84)	-1.71 (4.56)

Source: Table 14.2.1.1.11, Table 14.2.1.1.12, Table 14.2.1.1.13, Table 14.2.1.1.14, Table 14.2.1.1.5, Table 14.2.1.1.6, Table 14.2.1.1.18, Table 14.2.1.1.19, and Table 14.2.1.1.20
Baseline=[V1 score (D-14) + V2 score (D0)]/2
End of treatment (EoT)=[V6 score (D49) + V7 score (D56)]/2
BMI, body mass index

Figure 3: Change in the Mean Ullanlinna Narcolepsy Scale Total Score from Baseline to the End of Treatment (Full Analysis Set)



UNS total score by sex: For both male and female patients, the mean change from baseline to end of treatment in UNS total score was greater in the pitolisant group than the placebo group.

UNS total score by age: For patients aged <12 years and ≥12 years, the mean change from baseline to end of treatment in UNS total score was greater in the pitolisant group than the placebo group, although the difference between groups was smaller in the patients aged <12 years.

UNS total score by BMI: The mean change from baseline to end of treatment in UNS total score was greater in the pitolisant group than the placebo group for patients in the BMI normal and obese classes and was similar for patients in the BMI overweight class.

For the overall population, the mean (SD) UNS scores at baseline were 23.68 (9.08) in the placebo group and 24.63 (7.80) in the pitolisant groups. After 8 weeks of treatment, change from baseline to end of treatment in UNS total score was - 6.36 (8.59) in the pitolisant group (N=70) and -2.46 (5.55) in the placebo group (N=37), indicating a greater improvement in the pitolisant group compared with the placebo group (see Figure 3).

The applicant performed the subgroup analyses for the primary endpoint. In view of the results displayed in Table 5 above, the mean UNS change scores are rather consistent in each subgroup (sex, age and BMI) with those observed in the main analysis. Sex, age and/or BMI did seemingly have no influence on the UNS scores. However the evolution of UNS scores by sex, age and BMI should be interpreted with caution because of the low patient numbers in each subgroup and are only of descriptive value.

The primary analysis of the UNS total score between group comparisons in the FAS is summarized in Table 12. The UNS total score least squares (LS) mean (SE) of the adjusted difference from baseline to the end of treatment was -6.29 (1.14) in the pitolisant group and -2.60 (1.35) in the placebo group. The estimate LS means difference (SE) [95% CI] between treatment groups (pitolisant minus placebo) was -3.69 (1.37) [-6.38; -0.99], p=0.0073. The UNS total score change between pitolisant and placebo after an 8-week treatment period is statistically significant.

Table 12: Ullanlinna Narcolepsy Scale Total Severity Score – Between Group Comparison Main Analysis (Full Analysis Set)

				Difference in LS Means (Pitolisant minus Placebo)		
Treatment	**N**	**LS Mean (SE)[1]**	**95% CI**	**Estimate (SE)[2]**	**95% CI**	**p-value**
Pitolisant	72	-6.29 (1.14)	[-8.51; -4.06]	-3.69 (1.37)	[-6.38; -0.99]	0.0073
Placebo	38	-2.60 (1.35)	[-5.25; 0.05]			

Source: Table 14.2.1.1.21.

The UNS total score at the end of the double blind period, measured by the difference in LS means between pitolisant and placebo (-3.69 (1.37) [-6.38; -0.99]) shows that the difference is statistically significant (p=0.0073) and that pitolisant is superior to placebo for the primary outcome measure.

Some further analyses were conducted for the PPS and the difference in LS means between treatment groups (pitolisant minus placebo) was -4.01 (1.52) [-7.03; -0.98], p=0.0100.

The primary analysis results were supported by the results of all the sensitivity analyses of the UNS total score between group comparisons in the FAS (MNAR imputation [p = 0.0079], MAR imputation with centre as fixed effect [p = 0.0079], MAR imputation with interaction treatment-by-oxybate sodium intake [p = 0.0023], main model in patients without oxybate sodium intake [p = 0.0023], observed cases (i.e., completers) [p = 0.0071], and MAR imputation – actual treatment group [p = 0.0148]).

- Secondary endpoints

    1. Paediatric Daytime Sleepiness Scale (PDSS)

The mean (SD) change from baseline to end of treatment (EoT) in PDSS total score was -5.54 (5.31) in the pitolisant group (N=70) and -2.09 (6.47) in the placebo group (N=37), indicating a greater improvement in the pitolisant group compared with the placebo group (Table 13).

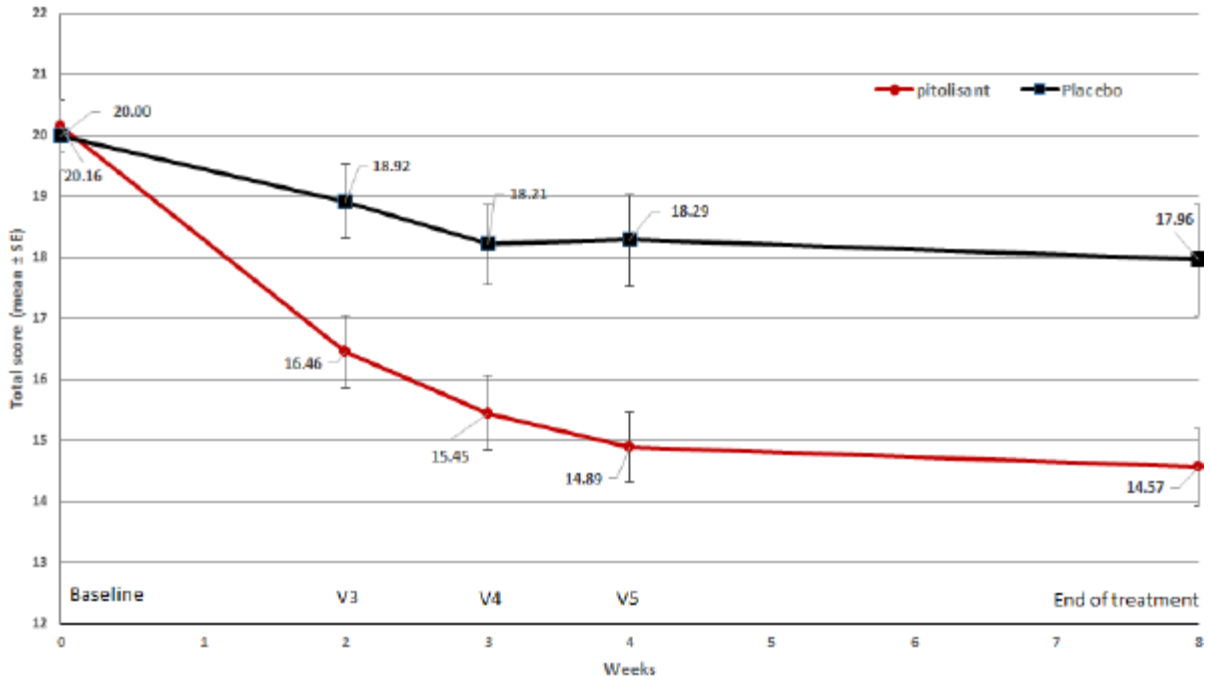
Table 13: Mean Change from Baseline to End of Treatment (EoT) – Paediatric Daytime Sleepiness Scale (PDSS) – Total score (FAS)

Treatment groups	Pitolisant	Placebo
Overall population		
N (baseline/EoT)	72/70	38/37
Baseline mean PDSS total score (SD)	20.16 (3.64)	20.00 (3.49)
EoT mean PDSS total score (SD)	14.57 (5.37)	17.96 (5.60)
Mean change from baseline (SD)	-5.54 (5.31)	-2.09 (6.47)

Source: Table 14.2.2.1.1, Table 14.2.2.1.3
Baseline=[V1 score (D-14) + V2 score (D0)]/2
End of treatment (EoT)=[V6 score (D49) + V7 score (D56)]/2

The evolution of mean ± SEM by visit of the PDSS total score is presented for the FAS in Figure 4 below.

Figure 4: Paediatric Daytime Sleepiness Scale Total Score – Evolution of the Mean (±SEM) from Baseline to End of Treatment (Full Analysis Set)



The analysis of the PDSS total score between group comparisons in the FAS is summarized in Table 14. The PDSS total score LS mean (SE) of the adjusted difference from baseline to the end of treatment was -5.53 (0.66) in the pitolisant group and -2.11 (0.89) in the placebo group. After 8 weeks of treatment, there was a statistically significant difference between pitolisant and placebo groups on the change in PDSS total score (LS means difference (SE) [95% CI]: -3.41 (1.07) [-5.52; -1.31], p = 0.0015).

Table 14: Paediatric Daytime Sleepiness Scale Total Score – Between Group Comparison Main Analysis (FAS)

				Difference in LS Means (Pitolisant minus Placebo)		
Treatment	**N**	**LS Mean (SE)[1]**	**95% CI**	**Estimate (SE)[2]**	**95% CI**	**p-value**
Pitolisant	72	-5.53 (0.66)	[-6.82; -4.23]	-3.41 (1.07)	[-5.52; -1.31]	0.0015
Placebo	38	-2.11 (0.89)	[-3.86; -0.37]			

Source: Table 14.2.2.1.5.

A greater proportion of patients in the pitolisant group (64.3% [45/70]) than in the placebo group (40.5% [15/37]) were **responders** according to the PDSS total score (i.e. patients with a change from baseline to end of treatment of at least 3 points on the PDSS). The estimated difference (23.75%; SE 9.90; 95%CI 4.35; 43.14) was statistically significant in favour of pitolisant after an 8 week treatment period (p=0.0186) as seen in Table 15 below:

Table 15: Paediatric Daytime Sleepiness Scale Total Score – Response to Treatment Between Group Comparison (FAS)

	Pitolisant (N=72)	Placebo (N=38)
At end of treatment[1]		
N	70	37
Response, n (%)	45 (64.3)	15 (40.5)
Inferential analysis		
Estimate (SE)[2]	23.75 (9.90)	
95% CI	[4.35; 43.14]	
p-value	0.0186	

Source: Table 14.2.2.1.8.

Response was defined as $PDSS_B$-$PDSS_F \geq 3$.

The mean (SD) change from baseline to end of treatment (EoT) in PDSS total score was -5.54 (5.31) in the pitolisant group (N=70) and -2.09 (6.47) in the placebo group (N=37), indicating a greater improvement in the pitolisant group compared with the placebo group

After analysis, the PDSS total score at the end of the double blind period, measured by the difference in LS means between pitolisant and placebo (-3.41 (1.07) [-5.52; -1.31]) shows that the difference is statistically significant (p=0.0015) and that pitolisant is superior to placebo for the treatment of daytime sleepiness associated with narcolepsy.

The rate of responder (i.e. patients with a change from baseline to end of treatment of at least 3 points on the PDSS) is of 64.3% [45/70] in the pitolisant group vs 40.5% [15/37] in the placebo group, which is statistically significant.

Similar results were observed in the PPS with a statistically significant difference in favour of pitolisant after an 8-week treatment period on the change in PDSS total score.

The main analysis results were also supported by the results of the sensitivity analyses (MNAR imputation [p=0.0021], observed cases (i.e., completers) [p=0.0020] and MAR imputation – actual treatment group [p=0.0031]).

2. UNS-Cataplexy (UNS-CTP) Subscore

In patients with type 1 narcolepsy, the mean (SD) change from baseline to end of treatment in UNS CTP subscore are displayed in Table 16.

Table 16: Mean Chane from Baseline to End of Treatment (EoT) – Ullanlinna Narcolepsy Scale Cataplexy subcore (FAS)

Treatment groups	Pitolisant	Placebo
Type I narcolepsy patients		
N (baseline/EoT)	61/60	29/28
Baseline mean UNS-CTP subscore (SD)	8.93 (3.96)	9.03 (4.33)
EoT mean UNS-CTP subscore (SD)	6.02 (4.00)	8.07 (4.62)
Mean change from baseline (SD)	-2.83 (3.96))	-1.27 (3.17)

Source: Table 14.2.2.2.1, Table 14.2.2.2.3
Baseline=[V1 score (D-14) + V2 score (D0)]/2
End of treatment (EoT)=[V6 score (D49) + V7 score (D56)]/2

The analysis of the UNS CTP subscore between group comparisons in patients with type 1 narcolepsy in the FAS using the LS means of the adjusted difference from baseline to the end of treatment is summarized in Table 17.

Table 17: Ullanlinna Narcolepsy Scale-Cataplexy Subcore – Between Group Comparison in Patients with Type I Narcolepsy Main Analysis (FAS)

				Difference in LS Means (Pitolisant minus Placebo)		
Treatment	N	LS Mean (SE)[1]	95% CI	Estimate (SE)[2]	95% CI	p-value
Pitolisant	61	-2.88 (0.44)	[-3.74; -2.02]	-1.77 (0.78)	[-3.29; -0.24]	0.0229
Placebo	29	-1.12 (0.64)	[-2.37; 0.13]			

Source: Table 14.2.2.2.5.

In patients with type 1 narcolepsy, the mean (SD) change from baseline to end of treatment in UNS CTP subscore was -2.83 (3.96) in the pitolisant group (N=60) and -1.27 (3.17) in the placebo group (N=28), indicating a greater improvement in the pitolisant group compared with the placebo group

There was a statistically significant difference in favour of pitolisant after the 8-week treatment period on the change in UNS CTP subscore in patients with type 1 narcolepsy (LS means difference (SE) [95% CI]: -1.77 (0.78) [-3.29; -0.24]; p = 0.0229).

The effect of pitolisant remained significant in the PPS (p = 0.0295) and in the sensitivity analyses in the FAS (MNAR imputation [p=0.0277], completers (observed cases) imputation [p=0.0284], MAR imputation – actual treatment group [p=0.0301]).

3. Weekly rate of cataplexie

In patients with type 1 narcolepsy, the decrease in the WRC was comparable between the two treatment groups. The difference between pitolisant and placebo groups on the WRC during the last week of the treatment period in the double-blind period was not significant, in patients with type 1 narcolepsy in the FAS (p = 0.0540).

As shown in Table 18 below, in the pitolisant group (N=61), the mean (SD) WRC during baseline, the stable dose period and during the last week of the treatment period was 8.63 (17.73), 6.81 (19.73) and 5.39 (16.52) episodes, respectively. In the placebo group (N=29), the mean (SD) WRC during baseline, the stable dose period and the last week of the treatment period, was 13.44 (26.92), 12.29 (22.79) and 10.73 (18.05) episodes, respectively. The decrease in the WRC was comparable between the two treatment groups.

Table 18: Patient Sleep diary – The weekly rate of cataplexy (WRC) – Description at each period – In type I Narcolepsy patients – Period in days – Periods calculated according to the first and last treatment intake dates – Full Analysis set

Baseline (D-14 to D0)	N	59	29
	Missing	2	0
	Mean (SD)	8.63 (17.73)	13.44 (26.92)
	Median	1.5	4.5
	[Q1 ; Q3]	[0.0 ; 9.5]	[0.5 ; 14.7]
	[Min ; Max]	[0.0 ; 88.0]	[0.0 ; 142.2]
Stable Dose Period (D28 to D56)	N	60	28
	Missing	1	1
	Mean (SD)	6.81 (19.73)	12.29 (22.79)
	Median	0.0	2.3
	[Q1 ; Q3]	[0.0 ; 3.3]	[0.0 ; 14.6]
	[Min ; Max]	[0.0 ; 121.9]	[0.0 ; 107.8]
Last Week of Treatment Period (D49 to D56)	N	60	28
	Missing	1	1
	Mean (SD)	5.39 (16.52)	10.73 (18.05)
	Median	0.0	1.8
	[Q1 ; Q3]	[0.0 ; 2.6]	[0.0 ; 14.0]
	[Min ; Max]	[0.0 ; 116.4]	[0.0 ; 75.3]

The analysis of the WRC during the last week of the treatment period in the double-blind phase (D49 to D56) between group comparisons in patients with type 1 narcolepsy in the FAS is summarized in Table 19 below.

Table 19: Patient Sleep diary – The weekly rate of cataplexy (WRC) – Between group Comparison – In type I Narcolepsy patients – Periods calculated according to the first and last treatment intake dates – Full Analysis set

		BF2.649 N=61	Placebo N=29
Number of events Last Week of Treatment Period (D49 to D56)	N	61	29
	Mean (SD)	5.44 (16.40)	10.70 (17.78)
	Median	0.0	1.8
	[Q1 ; Q3]	[0.0 ; 2.6]	[0.0 ; 11.8]
	[Min ; Max]	[0.0 ; 116.4]	[0.0 ; 75.3]
Main analysis (1)	LS means (SE)	2.14 (0.27)	5.05 (0.37)
	95% CI **	[1.26 ; 3.60]	[2.46 ; 10.38]
	E (SE)	0.42 (0.45)	
	95% CI ¤	[0.18 ; 1.01]	
	p-value	0.0540	
Sensitivity analysis : MNAR imputation (2)	LS means (SE)	2.05 (0.27)	4.57 (0.37)
	95% CI **	[1.20 ; 3.53]	[2.18 ; 9.49]
	E (SE)	0.45 (0.46)	
	95% CI ¤	[0.18 ; 1.11]	
	p-value	0.0831	
Sensitivity analysis : Observed cases (3)	N	60	28

The LS mean (SE) of the WRC during the last week of the treatment period was 2.14 (0.27) in the pitolisant group and 5.05 (0.37) in the placebo group. The rate defined as the ratio between the WRC found on pitolisant group and the WRC found on placebo group adjusted for baseline was 0.42 [95% CI: 0.18 to 1.01], p=0.0540. This difference is not significant.

The difference between pitolisant and placebo groups [2.14 (0.27) in the pitolisant group and 5.05 (0.37) in the placebo group] on the WRC during the last week of the treatment period in the double-blind phase (D49 to D56) was not significant (p=0.0540), in patients with type 1 narcolepsy in the FAS and similar results were observed in the analysis in patients with type 1 narcolepsy in the PPS. The results of the main analysis were confirmed in the sensitivity analyses in patients with type 1 narcolepsy in the FAS.

A complementary, post-hoc analysis was done on the most severe patients with regards to WRC. The proportion of patients with a WRC >15 decreased during the study in the pitolisant group and remained stable in the placebo group. Indeed, in the pitolisant group, a WRC >15 was reported for 16.9% of patients at baseline and 6.7% of patients during the last week of the treatment period. In the placebo group, a WRC >15 was reported for 24.1% of patients at baseline and 25.0% of patients during the last week of the treatment period. The value of this complementary, post-hoc analysis is only descriptive and does not allow to draw any robust conclusion. This could in particular not be used as a claim in the SmPC.

Moreover, considering a hierarchical strategy was used for strategy of controlling the test multiplicity, it is worth noting that any significant statistical result beyond this WRC criteria (i.e for the further secondary endpoints described below) cannot be taken into account and may only have a descriptive value. Since no statistically significant difference in WRC was observed between pitolisant and placebo, therefore no efficacy claim on the further criteria is possible from a methodological point of view which

is fortunately the case since clinical results as described in section 5.1 only refer to the primary endpoint.

Of note, in type 1 narcolepsy patients from the FAS, the proportion of patients with no cataplexy all along the study (D-14 to D63) was 23.0% in the pitolisant group and 20.7% in the placebo group.

4. Weekly frequency of cataplexy episodes

5. Maintenance of Wakefulness Test (MWT)

The MWT was used in this study to assess an individual's ability to remain awake while resisting the pressure to fall asleep. Patients were administrated four 30-minute MWT sessions at 2-hour intervals at the inclusion visit (V2) and at the endpoint visit (V7 or the last on-study visit).

In the FAS, the mean (SD) of sleep onset latency slightly increased during the study for patients in the pitolisant group and remained more or less stable for patients in the placebo group: in the pitolisant group, the mean (SD) of sleep onset latency was 10.14 (7.24) minutes at baseline and 11.47 (9.08) minutes at V7. In the placebo group, the mean (SD) of sleep onset latency was 10.61 (8.26) minutes at baseline and 10.19 (8.66) minutes at V7.

The MWT between group comparison of time to sleep onset analysis in the FAS is summarized in Table 20.

Table 20: Maintenance of Wakefulness – Between Group Comparison Time to Sleep Onset (FAS)

	Estimate (SE)	95% CI	p-value
MWT value at V2 (1)	-0.077 (0.016)	[-0.108; -0.045]	<0.001
Pitolisant versus placebo (1)	-0.29 (0.1)	[-0.484; -0.096]	0.004
Hazard ratio Pitolisant/Placebo (2)	0.748	[0.616; 0.903]	0.004

Source: Table 14.2.2.4.5.

According to the MAH, the results of the analysis of the MWT demonstrated favourable efficacy for pitolisant compared with placebo. The hazard ratio [95% CI] for the MWT time to sleep onset comparison between treatment groups (pitolisant minus placebo) was 0.748 [0.616; 0.903], p=0.004, meaning that at every moment of the MWT experiment, about 25% fewer patients in the pitolisant group compared with the placebo group fell asleep.

However, these results are only of descriptive value, all the more considering the hierarchical methodology of statistical tests.

6. Other efficacy parameters

The following exploratory efficacy endpoints have been analysed: UNS – Excessive Daytime Sleepiness (UNS-EDS) subscore, Clinical Global Impressions (CGI), Child and Adolescent Sleepiness Scale (CASS), Test of Everyday Attention for Children (TEA-Ch), Sleep parameters calculated from the patient sleep diary and Patient's Global Opinion (PGO) on the effect of treatment.

The favourable efficacy results for pitolisant compared with placebo on EDS reduction were also supported by exploratory efficacy endpoints measuring the changes in EDS (Child and Adolescent Sleepiness Scale [CASS] and UNS-EDS subscore), the severity of EDS assessed by the Investigator (Clinical Global Impression of Change [CGI-C]) and the comparison in patient's global opinion (PGO) on treatment effect at the EoT.

Summary of main study

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 21: Summary of Efficacy for trial P11-06

Title: Double-blind, multicentre, randomized, placebo-controlled trial to evaluate safety and efficacy of pitolisant in children from 6 to less than 18 years with narcolepsy with/without cataplexy, followed by a prolonged open-label period			
Study identifier	P11-06 - EudraCT Number: 2013-001506-29		
Design	This is a double-blind, multicenter, randomized, placebo-controlled study to evaluate the safety and efficacy of pitolisant in children aged from 6 to less than 18 years with narcolepsy with or without cataplexy meeting the International Classification of Sleep Disorders Third Edition (ICSD-3) criteria (narcolepsy type 1 and type 2). Patients were randomized to treatment with pitolisant or placebo in a 2:1 ratio at the end of the screening period at study inclusion. Randomization was stratified by study center. The study was planned to include 108 patients, more or less (at least 40%) equally balanced between age groups (6 to 11 years and 12 to 17 years) and sex.		
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:		8 weeks 28-day screening period that included a 2-week baseline period Data not yet available
Hypothesis	Superiority: The primary objective of this study is to compare pitolisant to placebo, with regard to EDS on the one hand, and to the number of cataplexy episodes, if any, on the other hand.		
Treatments groups	pitolisant		Pitolisant, 8 weeks, 72 patients randomized
	placebo		Placebo, 8 weeks, 38 randomized
	NA		NA
Endpoints and definitions	Primary endpoint	Changes in UNS	Changes in Ullanlinna Narcolepsy Scale (UNS) measuring the intensity and frequency of symptoms of narcolepsy (Excessive Daytime Somnolence and cataplexies), based on the change from baseline and at the end of double-blind period
	Key Secondary endpoint	Changes in PDSS	Changes in Excessive Daytime Somnolence (EDS) measured by the Paediatric Daytime Sleepiness Scale (PDSS) between baseline and the end of treatment. The PDSS is a sum score with 8 items leading to a score range of 0 to 32.
	Key Secondary endpoint	Changes in UNS-cataplexy	Changes in Ullanlinna Narcolepsy Scale-cataplexy (UNS-CTP) between baseline and the end of treatment. This subscore is defined as the sum of the first 4 items of the UNS
	Key Secondary endpoint	Changes in WRC	Changes in Weekly Rate of Cataplexy (WRC) i.e. differences in weekly frequency of cataplexy episodes, recorded in sleep diary by patient and/or parent/teacher
	Key Secondary endpoint	Changes in MWT	Changes in Maintenance of Wakefulness Test 30-Minute Version (MWT)
Database lock	15 Nov 2021		
Results and Analysis			
Analysis description	Primary Analysis		

Analysis population and time point description	**Full analysis set**, Change from baseline to the end of treatment defined by the end of double-blind period			
Descriptive statistics and estimate variability	Treatment group	pitolisant	placebo	
	Number of subject (UNS analysis)	72	38	
	Changes in UNS Least Square Mean (Standard Error) (1) 95% CI	-6.29 (1.14) [-8.51; -4.06]	-2.60 (1.35) [-5.25; 0.05]	
	Number of subject (PDSS analysis)	72	38	
	Changes in PDSS LS Mean (SE) (1) 95% CI	-5.56 (5.30) [-6.82 ; -4.23]	-2.11 (0.89) [-3.86 ; -0.37]	
	Number of subject (UNS-Cataplexy analysis in type I narcolepsy)	61	29	
	Changes in UNS-cataplexy LS Mean (SE) (1) 95% CI	-2.88 (0.44) [-3.74; -2.02]	-1.12 (0.64) [-2.37; 0.13]	
	Number of subject (WRC analysis in type I narcolepsy)	61	29	
	Changes in WRC LS Mean (SE) (2) 95% CI	2.14 (0.27) [1.26; 3.60]	5.05 (0.37) [2.46; 10.38]	
	Number of subject (MWT analysis)	72	38	
	Changes in MWT (Ratio)	Not available	Not available	
Effect estimate per comparison	UNS (primary endpoint) (1)	Comparison groups Difference in LS Means Estimate (SE) 95% CI P-value	Pitolisant minus Placebo -3.69 (1.37) [-6.38; -0.99] 0.0073	
	Changes in PDSS (1)	Comparison groups Difference in LS Means Estimate (SE) 95% CI P-value	Pitolisant minus Placebo -3.41 (1.07) [-5.52 ; -1.31] 0.0015	
	Changes in UNS-cataplexy (1)	Comparison groups Difference in LS Means Estimate (SE) 95% CI P-value	Pitolisant minus Placebo -1.77 (0.78) [-3.29; -0.24] 0.0229	
	Changes in WRC (2)	Comparison groups Difference in LS Means Estimate (SE) (2) 95% CI P-value	Pitolisant minus Placebo 0.42 (0.45) [0.18; 1.01] 0.0540	
	Changes in MWT (3)	Comparison groups Estimate Hazard Ratio 95% CI P-value	Pitolisant vs Placebo 0.748 [0.616; 0.903] 0.004	

Notes	(1) ANCOVA model, with a multiple imputation approach (MAR), including the fixed, categorical effects of treatment, and the continuous, fixed covariate of baseline and the random effect of center (2) Negative Binomial Regression model with a multiple imputation approach (MAR), including the fixed, categorical effects of treatment, and the continuous, fixed covariate of WRC baseline (3) Cox proportional regression model with MAR approach			
Analysis description	**Per Protocol set,** Change from baseline to the end of double-blind period			
Descriptive statistics and estimate variability	Treatment group	pitolisant	placebo	
	Number of subject primary endpoint (UNS analysis)	65	32	
	Changes in UNS Least Square Mean (Standard Error) (4) 95% CI	-6.65 (1.21) [-9.35; -3.96]	-2.65 (1.50) [-5.76; 0.47]	
	Number of subject (PDSS analysis)	65	32	
	Changes in PDSS LS Mean (SE) (4) 95% CI	-5.53 (0.66) [-6.83 ; -4.22]	-1.63 (0.94) [-3.50 ; 0.23]	
	Number of subject (UNS-Cataplexy analysis in type I narcolepsy)	56	24	
	Changes in UNS-cataplexy LS Mean (SE) (4) 95% CI	-2.95 (0.47) [-3.90 ; -2.01]	-1.03 (0.72) [-2.47 ; 0.41]	
	Number of subject (WRC analysis in type I narcolepsy)	56	24	
	Changes in WRC LS Mean (SE) (5) 95% CI	3.16 (0.24) [1.97 ; 5.10]	4.85 (0.36) [2.36 ; 9.87]	
	Number of subject (MWT analysis)	65	32	
	Changes in MWT (Ratio)	Not available	Not available	
Effect estimate per comparison	UNS (primary endpoint) (4)	Comparison groups Difference in LS Means Estimate (SE) 95% CI P-value	Pitolisant minus Placebo -4.01 (1.52) [-7.03; -0.98] 0.0100	
	Changes in PDSS (4)	Comparison groups Difference in LS Means Estimate (SE) 95% CI P-value	Pitolisant minus Placebo -3.89 (1.15) [-6.17 ; -1.62] 0.0010	
	Changes in UNS-cataplexy (4)	Comparison groups Difference in LS Means Estimate (SE) 95% CI P-value	Pitolisant minus Placebo -1.92 (0.87) [-3.64 ; -0.20] 0.0295	

	Changes in WRC (5)	Comparison groups Difference in LS Means Estimate (SE) 95% CI P-value	Pitolisant minus Placebo 0.65 (0.44) [0.27 ; 1.55] 0.3310
	Changes in MWT (3)	Comparison groups Estimate Hazard Ratio 95% CI P-value	Pitolisant vs Placebo 0.659 [0.431; 1.007] 0.056
Notes	(4) ANCOVA model, based on observed cases, including the fixed, categorical effects of treatment, and the continuous, fixed covariate of baseline and the random effect of center (5) Negative Binomial Regression model based on observed cases, including the fixed, categorical effects of treatment, and the continuous, fixed covariate of WRC baseline. (3) Cox proportional regression model with MAR approach		

2.4.2. Discussion on clinical efficacy

Design and conduct of clinical studies

P11-06 Study, a double-blind, multicentre, placebo-controlled, randomised-withdrawal design study provided some insights into the magnitude of effect of pitolisant that could be seen in children from 6 to less than 18 years with narcolepsy with/without cataplexy. The study comprised a 28-day screening period that included a 2-week baseline period, an 8-week double blind period and a 1-week single blind washout period and a currently ongoing prolonged open-label period with pitolisant treatment for patients willing to continue in the study.

Given the small population size and the rarity of the disease, the choice of this study design (pitolisant or placebo in a 2:1 ratio) was deemed appropriate, to ensure minimal exposure to placebo for a vulnerable population.

The inclusion and non-inclusion criteria are appropriate for the aim of the study. Patients were allowed to continue their anti-cataplectic drugs (including sodium oxybate) if they were at a stable dosage for at least 4 weeks before the inclusion visit and maintained at a stable dosage throughout the study.

There were three amendments whose main topics were to enhance twice the number of enrolled patients as well as to change the primary endpoint from Pediatric Daytime Sleepiness Scale (PDSS) to Ullanlinna Narcolepsy Scale (UNS), considered more reliable and specific for the paediatric population. The study was compliant with the PIP requirements and the requests regarding the SAP and the endpoint reversal between the primary and the key secondary endpoint were resolved.

A total of 110 patients were enrolled and randomized in the study: 72 patients in the pitolisant group and 38 patients in the placebo group and three patients withdrew consent and discontinued from the study (2 patients in the pitolisant group and 1 patient in the placebo group). The majority of patients (90 patients [81.8%]) had type 1 narcolepsy and 20 patients (18.2%) had type 2 narcolepsy reflecting the current epidemiology in paediatrics. Two thirds of the patients in the study were over 12 year of age.

Most patients received a daily dose of 20 mg (23.9%) or 40 mg (59.2%) whatever the age group. As recommended, no patient weighing <40 kg received a dose > 20 mg daily. For patients weighing ≥ 40 kg, the majority received a daily dose of 40 mg (72.4%).

Efficacy data and additional analyses

Regarding the primary endpoint, for the overall population, change from baseline to end of treatment in UNS total score was - 6.36 (8.59) in the pitolisant group (N=70) and -2.46 (5.55) in the placebo group (N=37), indicating a greater improvement in the pitolisant group compared with the placebo group. The UNS total score at the end of the double blind period, measured by the difference in LS means between pitolisant and placebo (-3.69 (1.37) [-6.38; -0.99]) shows that the difference is **statistically significant** (p=0.0073) and that pitolisant is superior to placebo for the primary efficacy outcome.

Some further analyses were conducted for the PPS and the difference in LS means between treatment groups (pitolisant minus placebo) was -4.01 (1.52) [-7.03; -0.98], p=0.0100. The primary analysis results were supported by the results of all the sensitivity analyses of the UNS total score between group comparisons in the FAS (MNAR imputation [p = 0.0079], MAR imputation with centre as fixed effect [p = 0.0079], MAR imputation with interaction treatment-by-oxybate sodium intake [p = 0.0023], main model in patients without oxybate sodium intake [p = 0.0023], observed cases (i.e., completers) [p = 0.0071], and MAR imputation – actual treatment group [p = 0.0148]).

Regarding the secondary endpoints:

- **PDSS**: The mean (SD) change from baseline to end of treatment in PDSS total score was -5.54 (5.31) in the pitolisant group (N=70) and -2.09 (6.47) in the placebo group (N=37), indicating a greater improvement in the pitolisant group compared with the placebo group. After analysis, the PDSS total score at the end of the double blind period, measured by the difference in LS means between pitolisant and placebo (-3.41 (1.07) [-5.52; -1.31]) shows that the difference is **statistically significant** (p=0.0015) and that pitolisant is superior to placebo for the treatment day time sleepiness associated with narcolepsy. The rate of responder (i.e. patients with a change from baseline to end of treatment of at least 3 points on the PDSS) is of 64.3% [45/70] in the pitolisant group vs 40.5% [15/37] in the placebo group, which is statistically significant. Similar results were observed in the PPS with a statistically significant difference in favour of pitolisant after an 8-week treatment period on the change in PDSS total score. The main analysis results were also supported by the results of the sensitivity analyses (MNAR imputation [p=0.0021], observed cases (i.e., completers) [p=0.0020] and MAR imputation – actual treatment group [p=0.0031]).
- **UNS-CTP**: In patients with type 1 narcolepsy, the mean (SD) change from baseline to end of treatment in UNS CTP subscore was -2.83 (3.96) in the pitolisant group (N=60) and -1.27 (3.17) in the placebo group (N=28), indicating a greater improvement in the pitolisant group compared with the placebo group. There was a **statistically significant** difference in favour of pitolisant after the 8-week treatment period on the change in UNS CTP subscore in patients with type 1 narcolepsy (LS means difference (SE) [95% CI]: -1.77 (0.78) [-3.29; -0.24]; p = 0.0229). The effect of pitolisant remained significant in the PPS (p = 0.0295) and in the sensitivity analyses in the FAS (MNAR imputation [p=0.0277], completers (observed cases) imputation [p=0.0284], MAR imputation – actual treatment group [p=0.0301]).
- **WRC**: The difference between pitolisant and placebo groups [2.14 (0.27) in the pitolisant group and 5.05 (0.37) in the placebo group] on the WRC during the last week of the treatment period in the double-blind phase (D49 to D56) **was not significant** (p=0.0540), in patients with type 1 narcolepsy in the FAS. A complementary, post-hoc analysis was done on the most severe

patients with regards to WRC. The proportion of patients with a WRC >15 decreased during the study in the pitolisant group and remained stable in the placebo group. Indeed, in the pitolisant group, a WRC >15 was reported for 16.9% of patients at baseline and 6.7% of patients during the last week of the treatment period. In the placebo group, a WRC >15 was reported for 24.1% of patients at baseline and 25.0% of patients during the last week of the treatment period. The value of this complementary, post-hoc analysis is only descriptive and does not allow to draw any robust conclusion. This could in particular not be used as a claim in the SmPC.

The Applicant provided clarification and justification to the uncertainties and limitations about favourable effects regarding the UNS.

First, the switch from the paediatric daytime sleepiness scale to the Ullanlinna narcolepsy scale score has been clarified and justified by the Applicant. Indeed, the design of the paediatric study focused on EDS and not on cataplexy, with the PDSS as the primary endpoint to evaluate in this population the change in EDS and not the cataplexy before changing the primary endpoint according to the efficacy results in 2015 of pitolisant on cataplexy in adults. Moreover, the Paediatric Daytime Sleepiness Scale (PDSS) as primary outcome in pediatrics was approved on 6 July 2012 by the PDCO and the detailed justification for the replacement of the PDSS by the Ullanlinna narcoleptic scale as the new primary endpoint was approved by the PDCO in June 2020 (EMEA-001176-PIP01-11-M05). Both endpoints were present since the beginning of the study.

Second, the data displaying a summarized comparison of metric characteristics of PDSS and UNS scales, show that the UNS scale seems more reliable than the PDSS scale, as an overall symptom measurement tool for narcolepsy, based on blinded data from 91 patients analyzed in Lehert 2022 and supplementary materials. In agreement with the Applicant's response, UNS scale can be considered as reliable: indeed, reliability is measured by the Cronbach alpha which is greater than 0.6 for the UNS scale of 0.80 [0.75, 0.85], and the intra-class correlation (ICC) which is close to 1, of 0.87. These two metrics for the UNS scale are higher than those for the PDSS scale with an alpha Cronbach of 0.72 [0.66, 0.76] and an ICC of 0.60. Moreover, the validity measured by the standardized sensitivity and correlation coefficient (R) with perceived status seem similar for both scales. The standardized sensitivity of the UNS scale of 0.55 [0.44, 0.59] is very close to that of the PDSS scale of 0.53 [0.43, 0.58]. The correlation coefficient of the UNS scale of 0.64 is close to that of the PDSS scale of 0.55.

Third, the determination of the minimal clinically important difference (MCID) of UNS total score of -3.3 and its 2 sub-scores were performed with a justification based on a statistical model (Lehert 2022 and supplementary materials) without argument and clinical data. However, based on standardized results (see statistical aspects below), a medium clinically relevant and statistically significant treatment effect has been observed with UNS and PDSS scales. It would have been preferable if the Applicant had mentioned the validation of the UNS scale in the pediatric population, based on Lehert 2022 and supplementary materials, as well as the MID for the total score of -3.3 and its 2 sub-scores, and also its reproducibility, even though it was not yet published, so that it would not have been the subject of a remark by the authorities.

Fourth, the validation of the UNS scale in the paediatric population is based on Lehert data and UNS proposed to the EMA as primary endpoint was endorsed by the PDCO in April 2020.

The Applicant substantiated the clinical relevance of the effect on cataplexy in type I narcolepsy patients, as measured by the qualitative Ullanlinna narcolepsy scale score and discussed the discrepancy between the paediatric and adult studies.

First, Lehert 2022 provided evidence that the UNS can be considered as a reliable and sensitive multi-symptom measurement tool with a minimal important difference (MID) of 3.3 for the UNS total score. In addition, authors established that the UNS-CTP sub-score allows the accurate and sensitive

measurement of cataplexy alone. Regarding that sub-score, they identified an MID of 1.5. In study P11-06, the analysis of the UNS-CTP sub-score between group comparison in type 1 narcolepsy patients from the FAS, showed a significant LS means difference (SE) [95% CI] between treatment groups (pitolisant minus placebo) of -1.77 (0.78) [-3.29; -0.24], p=0.0229. (P11-06 CSR Table 32) which reached the MID of 1.5 established by Lehert 2022.

Second, regarding the discrepancy on the cataplexy rate between the paediatric and adult studies, the Applicant provided overall acceptable arguments i.e.:

1) the inclusion criteria are not identical between the paediatric and adult studies (only NT1 for adult studies and NT1 / NT2 for paediatric study) with a more stringent and higher rate of cataplexy for inclusion in adult studies, and on the opposite a potential underestimation of the count of cataplexy episodes in the paediatric study

2) the adults' study P11-05 (the HARMONY CTP study) was sized and powered based on the WRC as the primary endpoint whereas in the paediatric study P11-06, it was sized and powered based on the UNS total score with WRC as a secondary endpoint,

3) although results on the WRC in the NT1 paediatric population remain in favour of pitolisant (rate Ratio of 0.42 [95% CI: 0.18 to 1.01], p=0.0540) it was close to significance,

4) a simple comparison of point estimate rate Ratio and 95%confidence interval results in adult studies of rR=0.52 [95%CI: 0.37 to 0.74] with results in the paediatric population of rR=0.42 [95% CI: 0.18 to 1.01] p=0.0540, did not show a difference between these two populations,

5) an initially post-hoc analysis performed on the most severe patients (WRC > 15) showed a similar decrease of the proportion of severe patients between pitolisant and placebo groups, for both adults and paediatrics (in adults, a reduction in the proportion of patients with a WRC >15, between baseline and the end of the study of 6.7% in pitolisant group vs 25.0% in placebo group and in paediatrics, a reduction in the proportion of patients with a WRC >15 , between baseline and the end of the study of 5.6% in pitolisant group vs 23.5% in placebo group).

Third, considering the relevance of the Ullanlinna narcolepsy scale in paediatric patients and especially its cataplexy subscore, whose positive result was not confirmed by the result on the secondary endpoint WRC, the Applicant justified that the UNS was developed by Hublin 1994, as a highly specific and sensitive qualitative and quantitative tool for assessing narcoleptic symptoms in comparison to the WRC, considered as only a quantitative tool for cataplexy episodes. The data based on the reference by Hublin 1994 have already been partially discussed previously and are considered acceptable.

The Applicant performed post-hoc subgroups' analyses to discuss the favourable effects of the primary endpoint (UNS) and the first key secondary endpoint (PDSS) in type I and II narcolepsy subgroups.

The CHMP agreed with the Applicant's interpretation from the descriptive post-hoc analyses. Indeed, in the overall population, the mean differences from baseline to the end of treatment for UNS and PDSS total scores were numerically greater and statistically significant in the pitolisant group (N=70) compared to the placebo group (N=37): for UNS scale -3. 90 (7.69), CI95%: -7.00, -0.80 and for PDSS scale -3. 45 (5.74), CI95%: -5.76, -1.14. These above described post-hoc results confirm the result of treatment effect observed in the FAS population previously assessed, in favour of the pitolisant group, in the primary analysis for UNS scale, -3. 69 (1.37), CI95%: -6.38, -0.99, p=0.0073, and -3. 41 (1.07) and for PDSS scale CI95%: -5.52, -1.31, p=0.0015.

Despite the lack of information of the precise statistical method used to estimate the CI95% related to the descriptive analyses on UNS and PDSS scores by type of Narcolepsy, the mean difference of UNS total score change from baseline to the end of treatment for the pitolisant group vs placebo group was

much lower and not statistically significant for type I narcolepsy (NT1) subgroup (N=88) -2.49 (7.24), CI95%: -5.78, 0.80 but significant statistically for type II narcolepsy (NT2) subgroup (N=19) -11. 04 (8.72), CI95%: -19.50, -2.59. Indeed, the small effect of pitolisant of --2.49 (7.24) for NT1 subgroup compared to -11.04 (8.72) for the NT2 subgroup may be explained as follows: The NT2 subgroup is very small (N=19) therefore the treatment effect based on a mean difference, is very sensitive to a few pitolisant patients very responders with extreme values of the UNS change from baseline (median (q1-q3):-5.25 (-31.50,-3.50)). However, the NT1 subgroup is four times larger (N=88) than the NT2 subgroup, therefore, the mean difference is less sensitive to a few patients treated by pitolisant with extreme values of the UNS change from baseline (median (q1-q3):-3.75 (-32.50,11.0)).

The PDSS total score results were comparable to the UNS total score but were statistically significant in the two subgroups, for NT1 subgroup, the mean difference was -2.45 (5.05), CI95%:-4.75, -0.15, and for NT2 subgroup of -8.94 (7.56), CI95%: -16.28, -1.61. The statistically significant treatment effect for both NT1 and NT2 subgroups for the PDSS total score shows that pitolisant is effective in both kinds of narcolepsy.

The Applicant provided new sensitivity analyses to ensure the lack of interaction between the type of narcolepsy and the treatment effect, measured by UNS total and PDSS scales. For this analysis, random meta-analytical model has been applied and the simple model was selected according to the Bayesian Information criterion (BIC). No significant heterogeneity of the treatment effect between NT1 and NT2 subgroups has been identified for UNS total score (I2=55%, $\chi 2$ test, p=0.136) and for PDSS total score (I2=45%, $\chi 2$ test, p=0.178). In agreement with the Applicant's response, these results support the effect of pitolisant vs placebo without significant heterogeneity across NT1 and NT2 subgroups.

In the complementary analysis, related to descriptive post-hoc analyses based on the severity of the disease (mild, moderate and severe) based on CGI-S at baseline, for UNS total and for PDSS scales, there is a benefit in favour of pitolisant for each severity subgroups which is not statistically significant. It could be related to a lack of power, due to small size of the subgroups.

As with the analysis by type of narcolepsy, the Applicant provided new sensitivity analyses to ensure the lack of interaction between the severity of the disease and the treatment effect, measured by UNS total and PDSS scales. For this analysis, random meta-analytical model has been applied and the simple model was selected according to the Bayesian Information criterion (BIC). No significant heterogeneity has been identified between the treatment effect of pitolisant and the severity of the disease for UNS scale and PDSS scale.

The Applicant provided an overview of the interactions between pitolisant and current concomitant treatments of narcolepsy (methylphenidate, modafinil, solriamfetol, sodium oxybate, dexamfetamine and venlafaxine) in the adult population by WHO preferred term, with no/low /medium risk of interaction.

The Applicant considered that these interactions could be extrapolated to the paediatric population i.e. children and adolescents which is agreed as there is no metabolic immaturity for involved metabolic pathways.

Overall, the anticipated medium risk of DDI between venlafaxine and pitolisant is already described in the current SmPC for Wakix® as follows: "CYP2D6 inhibitors: Co-administration of pitolisant with paroxetine significantly increases pitolisant mean C max and AUC0—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".

2.4.3. Conclusions on the clinical efficacy

The UNS total score at the end of the double blind period in the pivotal study shows that the difference is statistically significant (p=0.0073) and that pitolisant is superior to placebo for the primary efficacy outcome measure.

The PDSS total score at the end of the double blind period indicates a greater improvement in the pitolisant group compared with the placebo group which was statistically significant (p=0.0015) showing that pitolisant is superior to placebo the secondary efficacy outcome measure. The rate of responder (i.e. patients with a change from baseline to end of treatment of at least 3 points on the PDSS) is of 64.3% [45/70] in the pitolisant group vs 40.5% [15/37] in the placebo group, which is statistically significant.

In patients with type 1 narcolepsy, the change in UNS-CTP subscore in patients with type 1 narcolepsy shows a statistically significant difference in favour of pitolisant at the end of the double blind period (p = 0.0229).

The difference between pitolisant and placebo groups on the WRC was not significant (p=0.0540), in patients with type 1 narcolepsy. A complementary, post-hoc analysis was done on the most severe patients with regards to WRC. The value of this complementary, post-hoc analysis is only descriptive and does not allow to draw any robust conclusion.

Clinical safety

Patient exposure

All safety analyses were performed by actual treatment group in the Safety Set (i.e. all patient who received at least one treatment dose). The Safety Set included 73 patients in the pitolisant group and 37 patients in the placebo group. The provided data were collected up to the end of the Part 1 Double-Blind Period of the study (i.e., the 8-week randomized, double-blind period and the 1-week single-blind washout period).

The patient exposure is 73 paediatric patients in the pitolisant group and 37 paediatric patients in the placebo group.

Patients were exposed for 8 weeks to study treatment (double-blind period), and safety data were collected until 1 week after treatment discontinuation (washout period).

Adverse events

- **Brief Summary of Adverse Events**

All AEs (Adverse Events) were collected from the time the patient gave informed consent until 1 month after the last drug administration. A TEAE (Treatment-Emergent Adverse event) corresponded to an AE that occurred on or after first dose of treatment up to 7 days post-last dose.

See below an overview of AEs in the Safety Set:

Table 22: Overview of Adverse Events (Safety Set)

	Pitolisant (N=73)		Placebo (N=37)		All (N=110)	
	n (%)	No. of Events	n (%)	No. of Events	n (%)	No. of Events
At least one AE	25 (34.3)	71	13 (35.1)	31	38 (34.6)	102
At least one SAE	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0
At least one AE leading to study discontinuation	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0
At least one TEAE	22 (30.1)	60	13 (35.1)	29	35 (31.8)	89
At least one treatment-emergent SAE	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0
At least one treatment-related TEAE	14 (19.2)	35	8 (21.6)	12	22 (20.0)	47
At least one treatment-emergent treatment-related SAE	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0
At least one TEAE of severe intensity	2 (2.7)	3	0 (0.0)	0	2 (1.8)	3
At least one AESI	7 (9.6)	7	2 (5.4)	2	9 (8.2)	9

Source: Table 14.3.1.1.
AEs occurred during the study until V8.
TEAEs occurred during the double-blind period.
Abbreviations: AE=adverse event; AESI=adverse events of special interest; N=total number of patients; n=number of patients; No.=number; SAE=serious adverse event; TEAE=treatment-emergent adverse event; V=visit.

102 Adverse Events (AEs) were reported in 38 patients:

- 71 AEs in 25 patients (34.3%, 25/73) from the pitolisant group
- 31 AEs in 13 patients (31.1%, 13/37) from the placebo group

89 Treatment-Emergent Adverse Events (TEAEs) (corresponding to AEs that occurred on or after first dose of treatment up to 7 days post-last dose) were reported in 35 patients:

- 60 TEAEs in 22 patients (30.1%, 22/73) from the pitolisant group
- 29 TEAEs in 13 patients (35.1%, 13/37) from the placebo group

47 treatment-related TEAEs were reported in 22 patients:

- 35 treatment-related TEAEs in 14 patients (19.2%, 14/73) from the pitolisant group
- 12 treatment-related TEAEs in 8 patients (21.6%, 8/37) from the placebo group

There were no SAEs (Serious Adverse Events) reported during the study and no patients discontinued the study due to a TEAE.

9 Adverse Events of Special Interest (AESIs) were reported in 9 patients; all recovered:

- 7 AESIs in 7 patients (9.6%, 7/73) from the pitolisant group → "insomnia" (5 events), "dyspepsia" (1 event), and "anxiety" (1 event)
- 2 AESIs in 2 patients (5.4%, 2/37) from the placebo group → "insomnia" and "anxiety" (1 each)

The proportion of patients with at least 1 AE, 1 TEAE or 1 treatment-related TEAE was comparable between the two groups.

The proportion of patients with an AESI was higher in the pitolisant group. All reported AESIs are known frequent ADRs in the adult population (listed in the SmPC).

- **Brief Summary of Adverse Events by Age**

Patients aged 6-12 years

There were 22 patients aged < 12 years in the pitolisant group (30.1%, 22/73), and 13 in the placebo group (35.1%, 13/37).

The proportion of patients aged 6-12 years with at least 1 AE, 1 TEAE, 1 treatment-related TEAE or 1 AESI was lower in the pitolisant group.

Patients aged 12-18 years

There were 51 patients aged ≥ 12 years in the pitolisant group (69.9%, 51/73), and 24 in the placebo group (64.9%, 24/37).

The proportion of patients aged 12-18 years with at least 1 AE, 1 TEAE, 1 treatment-related TEAE or 1 AESI was higher in the pitolisant group.

3 TEAEs of severe intensity were reported, all in patients aged ≥ 12 years in the pitolisant group (see section *"Adverse Events by Severity"*).

- **Brief Summary of Adverse Events by Sex**

Male patients

There were 39 male patients in the pitolisant group (53.4%, 39/73), and 22 in the placebo group (59.5%, 22/37).

The proportion of male patients with at least 1 AE, 1 TEAE, 1 treatment-related TEAE or 1 AESI was lower in the pitolisant group.

Female patients

There were 34 female patients in the pitolisant group (46.6%, 34/73), and 15 in the placebo group (40.5%, 15/37).

The proportion of female patients with at least 1 AE, 1 TEAE, 1 treatment-related TEAE or 1 AESI was higher in the pitolisant group.

3 TEAEs of severe intensity were reported, all in female patients aged ≥ 12 years in the pitolisant group (see section *"Adverse Events by Severity"*).

- **Brief Summary of Adverse Events by Body Mass Index Class**

There were no patients in the BMI (body mass index) underweight class.

Patients in the BMI normal class

There were 30 patients in the BMI normal class in the pitolisant group (41.1%, 30/73), and 18 in the placebo group (48.6%, 18/37).

The proportion of patients in the BMI normal class with at least 1 AE or 1 TEAE was the same between the two groups.

The proportion of patients in the BMI normal class with at least 1 treatment-related TEAE or 1 AESI was higher in the pitolisant group.

Patients in the BMI overweight class

There were 19 patients in the BMI overweight class in the pitolisant group (26.0%, 19/73), and 7 in the placebo group (18.9%, 7/37).

The proportion of patients in the BMI overweight class with at least 1 AE or 1 treatment-related TEAE was higher in the pitolisant group.

The proportion of patients in the BMI overweight class with at least 1 TEAE was comparable between the two groups.

The proportion of patients in the BMI overweight class with at least 1 AESI was lower in the pitolisant group.

Patients in the BMI obese class

There were 24 patients in the BMI obese class in the pitolisant group (32.9%, 24/73), and 12 in the placebo group (32.4%, 12/37).

The proportion of patients in the BMI obese class with at least 1 AE, 1 TEAE or 1 treatment-related TEAE was lower in the pitolisant group.

The proportion of patients in the BMI obese class with at least 1 AESI was higher in the pitolisant group.

- **Most Frequently Reported Adverse Events**

The most frequently reported (≥5% of patients by treatment group) TEAEs reported in the Safety Set are summarized by SOC and PT in the below table:

Table 23: Most Frequently Reported (≥5% of Ptients) Treatment-Emergent Adverse Events by System Organ Class and preferred Term (Safety Set)

System Organ Class MedDRA Preferred Term	Pitolisant (N=73)		Placebo (N=37)		All (N=110)	
	n (%)	No. of Events	n (%)	No. of Events	n (%)	No. of Events
Nervous system disorders	14 (19.2)	28	4 (10.8)	6	18 (16.4)	34
Headache	14 (19.2)	24	3 (8.1)	4	17 (15.5)	28
Psychiatric disorders	11 (15.1)	11	4 (10.8)	4	15 (13.6)	15
Insomnia	5 (6.8)	5	1 (2.7)	1	6 (5.5)	6
Infections and infestations	3 (4.1)	4	7 (18.9)	9	10 (9.1)	13
Influenza	2 (2.7)	2	2 (5.4)	2	4 (3.6)	4
Upper respiratory tract infection	0 (0)	0	3 (8.1)	5	3 (2.7)	5
Gastrointestinal disorders	3 (4.1)	4	2 (5.4)	3	5 (4.5)	7
Diarrhoea	0 (0)	0	2 (5.4)	2	2 (1.8)	2

Source: Table 14.3.1.14.

TEAEs occurred during the double-blind period.

Abbreviations: MedDRA=Medical Dictionary for Regulatory Activities; N=total number of patients; n=number of patients; TEAE=treatment-emergent adverse event.

The most frequently reported (≥5% of patients overall) TEAEs were headache (15.5%) and insomnia (5.5%).

Overall, 28 events of "headache" were reported in 17 patients (15.5, 17/110):

- 24 events in 14 patients (19.2%, 14/73) from the pitolisant group

- 4 events in 3 patients (8.1%, 3/37) from the placebo group

Overall, 6 events of "insomnia" were reported in 6 patients (5.5, 6/110):
- 5 events in 5 patients (6.8%, 5/73) from the pitolisant group
- 1 event in 1 patient (2.7%, 1/37) from the placebo group

Overall, the most frequently reported AEs and TEAEs (corresponding to AEs that occurred on or after first dose of treatment up to 7 days post-last dose) were "headache" and "insomnia".

This is in line with the known safety profile in the adult population: the current SmPC for WAKIX indicates that the most frequent adverse drug reactions (ADRs) reported with pitolisant in adult patients were "insomnia" (8.4%) and "headache" (7.7%).

Besides the TEAEs of "headache" and "insomnia", another TEAE was reported in the pitolisant group: 2 events of "influenza" were reported in 2 patients.

No other TEAEs were reported in the pitolisant group.

- **Categorization of All Adverse Events**
    - **Adverse Events by Severity**

The majority of TEAEs were of mild (62/89 events, 69.7%) or moderate (24/89 events, 27.0%) intensity.

89 TEAEs were reported in 35 patients:
- 60 TEAEs in 22 patients (30.1%, 22/73) from the pitolisant group
    - 70% of the TEAEs in the pitolisant group were of mild intensity (reported in 27.4% of the patients, 20/73)
    - 25% of the TEAEs in the pitolisant group were of moderate intensity (reported in 11.0% of the patients, 8/73)
- 29 TEAEs in 13 patients (35.1%, 13/37) from the placebo group
    - 69% of the TEAEs in the placebo group were of mild intensity (reported in 27.0% of the patients, 10/37)
    - 31% of the TEAEs in the placebo group were of moderate intensity (reported in 16.2% of the patients, 6/37)

Three (3) TEAEs of severe intensity (5.0%) were reported by 2 patients (2.7%) in the pitolisant group (pyrexia and headache in 1 patient, insomnia in 1 patient). The 2 patients were in the group age ≥12 years old:

- The first case concerned a 16-year-old female patient with medical history of narcolepsy and severe obesity. She experienced severe pyrexia and headache, 19 days after pitolisant initiation. The events resolved on the same day with paracetamol. Pitolisant treatment was maintained and then the dose was increased, without recurrence of the events.
- The second case involved a 14-year-old female patient with narcolepsy, who presented severe insomnia 22 days after pitolisant initiation, with positive dechallenge.

Of the 2 cases reporting severe TEAEs, only the event of "insomnia" appears to be related to pitolisant (positive dechallenge). According to the current SmPC for WAKIX, "insomnia" is the most reported ADR in the adult population. This can be explained by the mechanism of action of pitolisant.

There were no TEAEs of severe intensity reported in the placebo group.

- **Adverse Events by Relationship to Treatment**

47 treatment-related TEAEs were reported in 22 patients:

- 35 treatment-related TEAEs in 14 patients (19.2%, 14/73) from the pitolisant group
- 12 treatment-related TEAEs in 8 patients (21.6%, 8/37) from the placebo group

The proportion of patients with at least 1 treatment-related TEAE was comparable between the two groups.

The most frequently reported treatment-related TEAEs in the pitolisant group were "headache" (11%), "insomnia" (5.5%) and "hypertension" (2.7%), respectively.

According to the current SmPC for WAKIX, the most frequent ADRs reported with pitolisant in adult patients were insomnia (8.4%) and headache (7.7%). In the SmPC, the ADR of "hypertension" is listed as uncommon (≥ 1/1,000 to < 1/100) in the adult population.

Data on treatment-related TEAEs are reassuring.

- **Adverse Events by Outcome**

There was 1 TEAE in 1 patient in the pitolisant group that was not resolved (pruritis of moderate intensity, not related to study treatment). All other TEAEs were resolved (88/89 events, 98.9%).

- **Adverse Events During the Stable Dose Period (V5 to V7)**

30 TEAEs were reported in 14 patients in the stable dose period:

- 15 TEAEs in 6 patients (8.2%, 6/73) from the pitolisant group
- 15 TEAEs in 8 patients (21.6%, 8/37) from the placebo group

The most frequently reported TEAEs in the stable dose period (more than in 1 patient from the safety set) were:

- Headache
  - 3 events in 2 patients (2.7%, 2/73) from the pitolisant group
  - 3 events in 3 patients (8.1%, 3/37) from the placebo group
- Cataplexy
  - 1 event in 1 patient (1.4%, 1/73) from the pitolisant group
  - 1 event in 1 patient (2.7%, 1/37) from the placebo group
- Somnolence
  - 2 events in 1 patient (1.4%, 1/73) from the pitolisant group
  - 1 event in 1 patient (2.7%, 1/37) from the placebo group
- Influenza
  - 2 events in 1 patient (1.4%, 1/73) from the pitolisant group
  - 1 event in 1 patient (2.7%, 1/37) from the placebo group
- Upper respiratory tract infection:
  - No event from the pitolisant group
  - 3 events in 2 patients (5.4%, 2/37) from the placebo group

All other TEAEs recorded in the stable dose period were each reported by 1 patient overall.

In the pitolisant group, the proportion of patients reporting TEAEs during the stable dose period was comparable in patients receiving daily 40 mg, 20 mg or 10 mg doses:

- 40 mg dose (n=42): 7 TEAEs were reported by 4 patients (9.5%);
- 20 mg dose (n=17): 3 TEAEs were reported by 2 patients (11.8%);
- 10 mg dose (n=11): 5 TEAEs were reported by 1 patient (9.1%).

The proportion of patients with at least 1 TEAE in the stable dose period was lower in the pitolisant group.

Serious adverse event/deaths/other significant events

There were no TEAEs leading to death and no SAEs.

Treatment-emergent AESI in the Safety Set are summarized by SOC and PT in the table below:

Table 24: Treatment-Emergent Aadverse Events of Special Interest by System Organ Class and Preferred Term (Safety Set)

System Organ Class MedDRA Preferred Term	Pitolisant (N=73)		Placebo (N=37)		All (N=110)	
	n (%)	No. of Events	n (%)	No. of Events	n (%)	No. of Events
Patients with at least 1 treatment-emergent AESI	7 (9.6)	7	2 (5.4)	2	9 (8.2)	9
Psychiatric disorders	6 (8.2)	6	2 (5.4)	2	8 (7.3)	8
Insomnia	5 (6.8)	5	1 (2.7)	1	6 (5.5)	6
Anxiety	1 (1.4)	1	1 (2.7)	1	2 (1.8)	2
Gastrointestinal disorders	1 (1.4)	1	0 (0)	0	1 (0.9)	1
Dyspepsia	1 (1.4)	1	0 (0)	0	1 (0.9)	1

Source: Table 14.3.1.21.

TEAEs occurred during the double-blind period.

Abbreviations: AESI=adverse events of special interest; MedDRA=Medical Dictionary for Regulatory Activities; N=total number of patients; n=number of patients; TEAE=treatment-emergent adverse event.

Overall, 9 patients (8.2%) reported 9 treatment-emergent AESI. The proportion of patients with treatment-emergent AESI was higher in the pitolisant group (7 patients [9.6%], 7 events) than in the placebo group (2 patients [5.4%], 2 events).

The most frequently reported AESI was insomnia, with 6 events reported in 6 patients (5.5%) overall. The proportion of patients with insomnia was higher in the pitolisant group (5 patients [6.8%], 5 events) than in the placebo group (1 patient [2.7%], 1 event). Only 1 event of insomnia was reported during the stable dosing period. The intensity of insomnia was severe for 1 patient (the patient was in the pitolisant group and the event was considered to be related to treatment), moderate for 2 patients, and mild for 3 patients. Insomnia was considered to be related to treatment for 4 events in the pitolisant group and for the event in the placebo group.

Anxiety was reported by 1 patient (1.4%) in the pitolisant group and 1 patient (2.7%) in the placebo group. These events were not reported during the stable dose period, were of mild intensity, and were considered to be related to study treatment.

Dyspepsia was reported by 1 patient (1.4%) in the pitolisant group. This event was not reported during the stable dose period, was of mild intensity, and was not considered to be related to study treatment.

The proportion of patients with an AESI was higher in the pitolisant group. However, all reported AESIs are known frequent ADRs in the adult population (listed in the current SmPC for WAKIX).

Laboratory findings

Haematology

Haematology results were normal for the majority of the patients. However, 1 patient in the pitolisant group presented a value of 102.0 g/L for hemoglobin at V7 (reported AE: "iron deficiency anaemia", mild intensity, not recovered), not considered related to study treatment.

Blood chemistry

There were no abnormal, clinically significant blood chemistry values.

Urinalysis

Urinalysis results were normal for the majority of the patients (expect for 1 patient in the placebo group, and the events recovered).

Urine test of drug abuse

Tests of drug abuse were all negative.

Serum pregnancy test

Pregnancy tests were all negative.

No abnormal laboratory values were considered to be related to treatment study.

- **Other observations related to safety**
    - **Vital Signs**

There were no notable changes in SBP, DBP, HR, or BMI during the study.

Hypertension of mild intensity, considered to be related to study treatment and noted as 'recovered without sequelae' for both patients, was reported as a TEAE in 2 patients in the pitolisant group. Hypertension was described in 1 female patient aged 17 years, in the BMI class overweight and height of 163 cm (corresponding to normal arterial pressure [SBP-DBP] <120-79 mmHg); she presented for 1 day, between V3 and V4 (at 10 mg daily) a slight increase of SBP (SBP-DBP, 122-78 mmHg), while at baseline her SBP was already abnormal (SBP-DBP, 122-68 mmHg). She normalized blood pressure without treatment during all following visits of study (except at V5, where SBP was 120 mmHg, below the baseline value). Another case of hypertension was reported in 1 male patient aged 16 years, in the BMI class normal range and height of 183 cm (corresponding to normal arterial pressure [SBP-DBP] <129-82 mmHg); he presented after 6 days of placebo treatment, between V7 and V8, arterial hypertension at SBP-DBP, 145-90 mmHg, improving 3 days later, at V8 with SBP-DBP, 131-86 mmHg. There was no anti-hypertensive medication prescribed but diet. To be noted, at baseline, his SBP was just above normal value for sex and height (SBP-DBP, 129-79 mmHg).

- **Electrocardiograms**

There were no notable changes in the ECG results during the study and all except 1 evaluable ECG which was was interpreted as abnormal, clinically significant in 1 patient in the pitolisant group at V5; the HR was decreased from 87 bpm at V1 to 59 bpm at V5 and there was no concomitant medication intake.

There were no patients with a QTcF post-dose >450 msec, a difference in QTcF post-dose versus pre-dose ≥60 msec, or QT post-dose ≥500 msec during the study.

- **Childhood Depression Inventory (CDI)**

The CDI scale is a 27-item self-administrated questionnaire commonly used in research to assess depression. The short version of 12 items was used in the study. The patient was asked to pick out the statement in each of the items which best described the way he/she felt right now at the moment of the assessment. The range of scores for the scale are 0-3=none or minimal; 4-7=mild; 8-15=moderate; ≥ 16=severe depression.

The mean (SD) CDI total score decreased during the double-blind period of the study for patients overall and in each treatment group:

- The mean (SD) CDI total score for all patients was 4.2 (3.3) at baseline and 3.6 (3.0) at V6;
- The mean (SD) CDI total score for patients in the pitolisant group was 4.4 (3.5) at baseline and 3.6 (3.2) at V6;
- The mean (SD) CDI total score for patients in the placebo group was 3.8 (3.0) at baseline and 3.5 (2.8) at V6.

The mean (SD) CDI total score at V8 after the 1-week washout period was decreased from baseline for patients in both the pitolisant group (4.0 [3.7]) and the placebo group (3.1 [2.7]).

The CDI range of scores is presented for the Safety Set in the below table:

Table 25: Childhood Depression Inventory – Range of Final Score (Safety Set)

	Pitolisant (N=73)	Placebo (N=37)	All (N=110)
Baseline			
N	73	37	110
None or minimal depression, n (%)	34 (46.6)	16 (43.2)	50 (45.5)
Mild depression, n (%)	24 (32.9)	17 (45.9)	41 (37.3)
Moderate depression, n (%)	15 (20.5)	4 (10.8)	19 (17.3)
Severe depression, n (%)	0 (0.0)	0 (0.0)	0 (0.0)
Visit 6			
N	71	36	107
None or minimal depression, n (%)	41 (57.7)	19 (52.8)	60 (56.1)
Mild depression, n (%)	20 (28.2)	15 (41.7)	35 (32.7)
Moderate depression, n (%)	10 (14.1)	2 (5.6)	12 (11.2)
Severe depression, n (%)	0 (0.0)	0 (0.0)	0 (0.0)
Visit 8			
N	69	36	105
Missing	1	0	1
None or minimal depression, n (%)	39 (56.5)	22 (61.1)	61 (58.1)
Mild depression, n (%)	15 (21.7)	12 (33.3)	27 (25.7)
Moderate depression, n (%)	15 (21.7)	2 (5.6)	17 (16.2)
Severe depression, n (%)	0 (0.0)	0 (0.0)	0 (0.0)

Source: Table 14.3.6.2.
0-3=none or minimal; 4-7=mild; 8-15=moderate; ≥16=severe depression.
Abbreviations: N=total number of patients; n=number of patients.

The percentage of patients reporting none or minimal depression increased from baseline during the study:

- Patients overall: 45.5% of patients at baseline and 56.1% of patients at V6;

- Pitolisant group: 46.6% of patients at baseline and 57.7% of patients at V6;
- Placebo group: 43.2% of patients at baseline and 52.8% of patients at V6.

The percentage of patients reporting none or minimal depression at V8 after the 1-week washout period was increased from baseline for patients in both the pitolisant group (56.5%) and the placebo group (61.1%).

The percentage of patients reporting mild depression was decreased from baseline during the study:

- Patients overall: 37.3% of patients at baseline and 32.7% of patients at V6;
- Pitolisant group: 32.9% of patients at baseline and 28.2% of patients at V6;
- Placebo group: 45.9% of patients at baseline and 41.7% of patients at V6.

The percentage of patients reporting mild depression at V8 after the 1-week washout period was decreased from baseline for patients in both the pitolisant group (21.7%) and the placebo group (33.3%).

Moderate depression at baseline was reported by a higher proportion of patients in the pitolisant group (20.5%) than in the placebo group (10.8%). At V6, the proportion of patients reporting moderate depression was decreased from baseline in both the pitolisant group (14.1%) and the placebo group (5.6%). The percentage of patients reporting moderate depression at V8 after the 1-week washout period was similar to baseline for patients in the pitolisant group (21.7%) and decreased from baseline in the placebo group (5.6%).

There were no patients with severe depression according to the CDI.

- **Columbia-Suicide Severity Rating Scale**

The Columbia-Suicide Severity Rating Scale (C-SSRS) was evaluated at all visits of the study and used by individuals who have received training. Ultimately, the determination of the presence of suicidal ideation or behavior depends on the judgment of the individual administering the scale. The C-SSRS was described, in terms of Suicidal risk (Yes/No), at baseline and at each post-baseline visit.

All except 3 patients were determined not to have engaged in any suicidal behavior and/or ideation during the study. Three (3) patients (1 patient in the pitolisant group, 2 patients in the placebo group) were considered to be at suicide risk during the study: 1 patient in the placebo group at V3, 1 patient in the pitolisant group at V7, and 1 patient in the placebo group at V7. These patients all declared no suicide risk at the following study visits, without anti-depressant treatment.

- **Withdrawal Symptoms Questionnaire (DSM IV)**

The amphetamine-like withdrawal symptoms questionnaire was used during a placebo wash-out week after the abrupt interruption of study drug intake at the end of the double-blind treatment period, on two occasions: 3 days after the interruption by phone (T1) and 7 days after the interruption during the last visit (V8).

According to the DSM IV, an amphetamine-like withdrawal syndrome is confirmed if during the first days following the abrupt discontinuation of study treatment dysphoria appears accompanied by at least two symptoms among fatigue, increased appetite, insomnia or hypersomnia, psychomotor retardation or agitation, and vivid and unpleasant dreams.

At both T1 (3 days after the interruption) and V8 (7 days after the interruption), the proportion of patients reporting each withdrawal symptom was higher in the pitolisant group.

However, the proportion was similar:

- For "dysphoria" at T1 (11.5% in the pitolisant group; 9.4% in the placebo group)
- For "psychomotor retardation or agitation" at T1 (8.2% in the pitolisant group; 6.3% in the placebo group)
- For "fatigue" at V8 (30.0% in the pitolisant group; 27.8% in the placebo group)

In the pitolisant group, the most frequently reported withdrawal symptoms were: "insomnia or hypersomnia" (27.9% at T1 and 30.0% at V8) and "fatigue" (26.2% at T1 and 30.0% at V8).

The proportion of patients who met the definition of amphetamine-like withdrawal syndrome was higher in the pitolisant group at T1 and V8:

- Pitolisant group: 9.6% at T1 and 16.4% at V8
- Placebo group: 5.4% at T1 and 8.1% at V8

Discontinuation due to adverse events

There were no discontinuations due to AEs.

2.4.4. Discussion on clinical safety

The patient exposure in study P11-06 is 73 paediatric patients in the pitolisant group and 37 paediatric patients in the placebo group. Patients were exposed for 8 weeks to study treatment (double-blind period), and safety data were collected until 1 week after treatment discontinuation (washout period).

Between baseline and after the 1-week washout period, the proportion of patients from the pitolisant group in the range "none or minimal depression" increased. The proportion of patients in the range "mild depression" decreased, and remained similar in the range "moderate depression". Detailed analysis of comorbidity depression was provided and showed that overall throughout the study, the CDI score for patients in both group (pitolisant and placebo) decreased However globally, the mean CDI score was higher in the pitolisant group, but remained in the range "none or minimal" or "mild".

Regarding the assessment of withdrawal symptoms, the proportion of patients reporting each withdrawal symptom was higher in the pitolisant group than in the placebo group, both 3 days and 7 days after pitolisant discontinuation. In the pitolisant group, the most frequently reported withdrawal symptoms were: "insomnia or hypersomnia" and "fatigue". The proportion of patients who met the definition of amphetamine-like withdrawal syndrome was higher in the pitolisant group than in the placebo group, both 3 days and 7 days after pitolisant discontinuation. Pitolisant may induce withdrawal syndrome; however the difference in the proportion of patients with amphetamine-like withdrawal syndrome was not significant (Chi-2 test, p=0.229).

No new safety concern emerged from the paediatric population in the P11-06 study. The safety profile for pitolisant seems similar between the adult and paediatric populations. There were no deaths, no SAEs and no patient discontinued the treatment due to AEs. The most frequently reported AEs were "headache" and "insomnia" (respectively in 11% and 5.5% of the patient in the pitolisant group). This is in line with the known safety profile in the adult population.

Regarding the severity of AEs, the proportion of AEs of mild or moderate intensity was comparable between the pitolisant group and the placebo group. Of the 2 cases reporting severe AEs, both in the pitolisant group (events of pyrexia and headache in 1 patient, and event of insomnia in another patient),

only the event of "insomnia" appears to be related to pitolisant (positive dechallenge). This is consistent with the mechanism of action of the substance.

No abnormal laboratory values were considered to be related to treatment study.

2.4.5. Conclusions on clinical safety

This assessment of safety has not identified new risks in children/adolescents regarding the use of pitolisant. In the P11-06 study, the safety profile in paediatric population appears to be comparable to the safety profile in adult population.

The present type II variation lacks robust safety information on long-term follow-up although some interim long-term safety data (up to 72 months) from the open-label extension study currently ongoing in paediatric patients have been provided over the course of the assessment.

"Long-term safety" is already a missing information in the RMP and PSURs and will be also applicable to paediatric population. The RMP was updated accordingly.

2.4.6. PSUR cycle

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

2.5. Risk management plan

The MAH submitted an updated RMP version with this application.

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

The PRAC considered that the risk management plan version 7.1 is acceptable.

The CHMP endorsed this advice without changes.

Safety concerns

Important identified risks	Insomnia Gastric disorders caused by hyperacidity Anxiety Depression and suicidal ideation Weight increase
Important potential risks	Proconvulsive potential QT-interval prolongation Misuse Drug dependence Rebound effect Fertility disorders Exposure during pregnancy and lactation Interaction with drugs displaying histamine H1 receptor antagonism activity.

Missing information	Long-term safety, including paediatric patients Patients with severe depression and severe anxiety Patients with underlying severe cardiovascular diseases

Pharmacovigilance plan

Study short name and title	**P15-11:** A multi-center, observational **post-authorization safety** study to document the drug utilization of Wakix® and to collect information on the **safety** of Wakix® when used in routine medical practice	
Rationale and study objectives	• To collect safety information on the long-term safety of Wakix when used in real-life setting in adult population • To document the drug utilization patterns of Wakix in routine medical practice	
Study design	International, non-interventional open-label prospective multicenter long-term post-authorization safety study (PASS). The patients will be observed during routine clinical practice up to five years	
Study population	Adult patients being prescribed Wakix® according to the SmPC for treatment initiation of narcolepsy with or without cataplexy	
Milestones	Protocol submission	04/02/2016
	PRAC decision adopted on	02/09/2016
	Study start (FPFV)	15/12/2016
	Study finish (LPLV)	Q2 2024
	Final report	Q1 2025

Risk minimisation measures

Safety concern	**Risk minimisation measures**	**Pharmacovigilance activities**
Insomnia	Routine risk minimisation SmPC § 4.8 PL Section 4 No additional minimisation measure Other routine risk minimization measures Wakix is subject to restricted medical prescription. Treatment should be initiated by a physician experienced in the treatment of sleep disorders.	There are no **additional** pharmacovigilance activities and there are **no** routine pharmacovigilance activities beyond adverse reactions reporting and signal detection.
Gastric disorders caused by hyperacidity	Routine risk minimization SmPC § 4.4 SmPC § 4.8 PL section 2 PL section 4 No additional minimisation measure Other routine risk minimization measures Wakix is subject to restricted medical prescription. Treatment should be initiated by a physician experienced in the treatment of sleep disorders.	There are no **additional** pharmacovigilance activities and there are **no** routine pharmacovigilance activities beyond adverse reactions reporting and signal detection.
Anxiety	Routine risk minimization SmPC § 4.4	There are no **additional** pharmacovigilance activities and there are **no** routine

Safety concern	Risk minimisation measures	Pharmacovigilance activities
	SmPC § 4.8 PL section 2 PL section 4 No additional minimisation measure . Other routine risk minimization measures Wakix is subject to restricted medical prescription. Treatment should be initiated by a physician experienced in the treatment of sleep disorders.	pharmacovigilance activities beyond adverse reactions reporting and signal detection.
Depression and suicidal ideation	Routine risk minimisation SmPC § 4.4 SmPC § 4.8 PL section 2 PL section 4 No additional minimisation measure Other routine risk minimization measures Wakix is subject to restricted medical prescription. Treatment should be initiated by a physician experienced in the treatment of sleep disorders.	There are no **additiona**l pharmacovigilance activities. Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: specific adverse reaction follow-up questionnaire.
Weight increase	Routine risk minimisation SmPC § 4.4 SmPC § 4.8 PL section 2 PL section 4 No additional risk minimisation measure Other routine risk minimization measures Wakix is subject to restricted medical prescription. Treatment should be initiated by a physician experienced in the treatment of sleep disorders.	There are no **additional** pharmacovigilance activities and there are **no** routine pharmacovigilance activities beyond adverse reactions reporting and signal detection.
Proconvulsive potential	Routine risk minimisation SmPC § 4.4 SmPC § 5.3 PL section 2 No additional risk minimisation measure. Other routine risk minimization measures Wakix is subject to restricted medical prescription. Treatment should be initiated by a physician experienced in the treatment of sleep disorders.	There are no **additional** pharmacovigilance activities and there are **no** routine pharmacovigilance activities beyond adverse reactions reporting and signal detection.
QT-interval prolongation	Routine risk minimisation SmPC § 4.4	There are no **additional** pharmacovigilance activities and there are **no** routine

Safety concern	Risk minimisation measures	Pharmacovigilance activities
	SmPC § 4.5 SmPC § 4.8 SmPC § 5.3 PL sections 2 and 4 No additional minimisation measure Other routine risk minimization measures Wakix is subject to restricted medical prescription. Treatment should be initiated by a physician experienced in the treatment of sleep disorders.	pharmacovigilance activities beyond adverse reactions reporting and signal detection.
Misuse	Routine risk minimisation SmPC § 4.2 SmPC § 5.3 No additional risk minimisation measure Other routine risk minimization measures Wakix is subject to restricted medical prescription. Treatment should be initiated by a physician experienced in the treatment of sleep disorders.	There are no **additional** pharmacovigilance activities and there are **no** routine pharmacovigilance activities beyond adverse reactions reporting and signal detection.
Drug dependence	Routine risk minimisation SmPC § 4.2 SmPC § 5.3 No additional risk minimisation measure Other routine risk minimization measures Wakix is subject to restricted medical prescription. Treatment should be initiated by a physician experienced in the treatment of sleep disorders.	There are no **additional** pharmacovigilance activities and there are **no** routine pharmacovigilance activities beyond adverse reactions reporting and signal detection.
Rebound effect	Routine risk minimisation SmPC § 4.2 SmPC § 4.4 No additional risk minimisation measure Other routine risk minimization measures Wakix is subject to restricted medical prescription. Treatment should be initiated by a physician experienced in the treatment of sleep disorders.	There are no **additional** pharmacovigilance activities and there are **no** routine pharmacovigilance activities beyond adverse reactions reporting and signal detection.
Fertility disorders	Routine risk minimisation SmPC § 4.6 SmPC § 5.3 No additional risk minimisation measure Other routine risk minimization measures Wakix is subject to restricted medical prescription. Treatment should be	There are no **additional** pharmacovigilance activities and there are **no** routine pharmacovigilance activities beyond adverse reactions reporting and signal detection.

Safety concern	Risk minimisation measures	Pharmacovigilance activities
	initiated by a physician experienced in the treatment of sleep disorders.	
Exposure during pregnancy and lactation	Routine risk minimisation SmPC § 4.3 SmPC § 4.4 SmPC § 4.5 SmPC § 4.6 SmPC § 5.3 PL Section 2 No additional risk minimisation measure Other routine risk minimization measures Wakix is subject to restricted medical prescription. Treatment should be initiated by a physician experienced in the treatment of sleep disorders.	There are no **additional** pharmacovigilance activities and there are **no** routine pharmacovigilance activities beyond adverse reactions reporting and signal detection.
Interaction with drugs displaying histamine H1 receptor antagonism activity.	Routine risk minimisation SmPC § 4.5 PL Section 2 No additional risk minimisation measure Other routine risk minimization measures Wakix is subject to restricted medical prescription. Treatment should be initiated by a physician experienced in the treatment of sleep disorders.	There are no **additional** pharmacovigilance activities and there are **no** routine pharmacovigilance activities beyond adverse reactions reporting and signal detection.
Long-term safety including paediatric patients	Routine risk minimisation SmPC § 4.8 PL section 4 No additional risk minimisation measure Other routine risk minimization measures Wakix is subject to restricted medical prescription. Treatment should be initiated by a physician experienced in the treatment of sleep disorders.	There are **no** routine pharmacovigilance activities beyond adverse reactions reporting and signal detection. Additional Pharmacovigilance activities to assess the long-term safety of pitolisant in adult population (PASS P15-11, Category 1) and paediatric population (open-label extension study from the paediatric clinical trial (P11-06, Category 3).
Patients with severe depression and severe anxiety.	Routine risk minimisation SmPC § 4.4 PL Section 2 No additional risk minimisation measure Other routine risk minimization measures Wakix is subject to restricted medical prescription. Treatment should be initiated by a physician experienced in the treatment of sleep disorders.	There are **no** routine pharmacovigilance activities beyond adverse reactions reporting and signal detection. Additional Post-Authorisation Safety Study to assess the long-term safety of pitolisant: Study short name: **P15-11:** 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 study report planned for 2025

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Patients with underlying severe cardiovascular disease	Routine risk minimisation SmPC § 4.4 PL Section 2 No additional risk minimisation measure Other routine risk minimization measures Wakix is subject to restricted medical prescription. Treatment should be initiated by a physician experienced in the treatment of sleep disorders.	There are no **additional** pharmacovigilance activities and there are **no** routine pharmacovigilance activities beyond adverse reactions reporting and signal detection.

2.6. Update of the Product information

As a consequence of this new indication, sections 4.1, 4.2, 4.4, 4.8, 5.1 and 5.2 of the SmPC have been updated. The Package Leaflet has been updated accordingly.

2.6.1. User consultation

No justification for not performing a full user consultation with target patient groups on the package leaflet has been submitted by the MAH. However, the changes to the package leaflet are minimal and do not require user consultation with target patient groups.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

Narcolepsy is a rare, chronic neurological disorder, frequently occurring from childhood and persisting through adolescence and adulthood. The prevalence of narcolepsy in childhood is not known but can be estimated from adult studies to be greater than 0.02% to 0.06% in Western countries. Initial symptoms of narcolepsy occur before the age of 18 in over 50% of patients and may start at a very young age also before puberty onset, often with similar but stronger symptoms than in adults.

The diagnosis criteria have been defined in the revised International Classification of Sleep Disorders (ICSD- 3, AASM 2014) and separate the narcolepsy with cataplexy (Type 1) and the narcolepsy without cataplexy (Type 2).

The presentation of narcolepsy can be very variable, making the diagnosis difficult. Narcolepsy is a long-term sleep disorder which affects the brain's ability to regulate the normal sleep-wake cycle. This leads to symptoms such as an irresistible urge to sleep, even at inappropriate times and places, and disturbed night-time sleep. Some patients also have episodes of severe muscle weakness (cataplexy) that can cause collapse. Narcolepsy occurs during childhood in combination with cataplexy in two-thirds of patients. Symptoms may develop rapidly over a few weeks or months, with excessive daytime sleepiness (EDS) and cataplexy being the most dramatic and observable symptoms.

Paediatric narcolepsy is also associated with comorbidities including rapid weight gain, precocious puberty, and ADHD (recently published systematic review of the literature showed that more than 30%

of children with narcolepsy presented symptoms of ADHD [Kim et al. 2020]), and increased risk for deficits in social functioning, depression, and anxiety. School performance is also typically impaired.

Therefore, the burden of this disorder in children is higher than in adults. Consequently, an early diagnosis with appropriate treatment, is fundamental to allow children or adolescents with narcolepsy to potentially reach a normal school performance and to reduce social impairment.

3.1.2. Available therapies and unmet medical need

According to guidelines published by the European task force, management of narcolepsy with or without cataplexy relies on several classes of drugs, namely stimulants (amphetamine and non-amphetamine like methylphenidate) for EDS, wake-promoting agents such as modafinil, histamine receptor antagonists such as pitolisant in adults, antidepressants for cataplexy, and hypno-sedative drugs for disturbed nocturnal sleep. However, the use of some of these treatments may be limited due to off-label use or by associated adverse effects and because the dosing regimen may require a nocturnal intake for children.

Cataplexy may be managed off label with serotonin reuptake inhibitors (fluoxetine), tricyclic antidepressants (clomipramine), or selective norepinephrine reuptake inhibitors (venlafaxine). Cataplexy can also be managed with sodium oxybate in paediatrics > 7 years of age. However sodium oxybate has high potential for abuse and respiratory depression and sedation that require careful oversight, in particular in paediatrics. Considering the current unmet medical need in the management of narcolepsy in paediatric population, combination therapies including pitolisant could be an interesting option for treatment of EDS with or without cataplexy to expand the treatment panel options, all the more that pitolisant showed absence or low abuse potential according to clinical data.

3.1.3. Main clinical studies

P11-06 Study, a double-blind, multicentre, placebo-controlled, randomised-withdrawal design study provided some insights into the magnitude of effect of pitolisant that could be seen in children from 6 to less than 18 years with narcolepsy with/without cataplexy. The study comprised a 28-day screening period that included a 2-week baseline period, an 8-week double blind period and a 1-week single blind washout period and a currently ongoing prolonged open-label period with pitolisant treatment for patients willing to continue in the study.

A total of 110 patients were enrolled and randomized in the study: 72 patients in the pitolisant group and 38 patients in the placebo group and three patients withdrew consent and discontinued from the study (2 patients in the pitolisant group and 1 patient in the placebo group). The majority of patients (90 patients [81.8%]) had type 1 narcolepsy and 20 patients (18.2%) had type 2 narcolepsy reflecting the current epidemiology in paediatrics. Two thirds of the patients in the study were over 12 year of age.

Most patients received a daily dose of 20 mg (23.9%) or 40 mg (59.2%) whatever the age group. As recommended, no patient weighing <40 kg received a dose > 20 mg daily. For patients weighing ≥ 40 kg, the majority received a daily dose of 40 mg (72.4%).

3.2. Favourable effects

Regarding the primary endpoint, for the overall population, change from baseline to end of treatment in UNS total score was - 6.36 (8.59) in the pitolisant group (N=70) and -2.46 (5.55) in the placebo group (N=37), indicating a greater improvement in the pitolisant group compared with the placebo group. The UNS total score at the end of the double blind period, measured by the difference in LS means between

pitolisant and placebo (-3.69 (1.37) [-6.38; -0.99]) shows that the difference is **statistically significant** (p=0.0073) and that pitolisant is superior to placebo for the primary efficacy outcome measure.

Further analyses were conducted for the PPS and the difference in LS means between treatment groups (pitolisant minus placebo) was -4.01 (1.52) [-7.03; -0.98], p=0.0100. The primary analysis results were supported by the results of all the sensitivity analyses of the UNS total score between group comparisons in the FAS (MNAR imputation [p = 0.0079], MAR imputation with centre as fixed effect [p = 0.0079], MAR imputation with interaction treatment-by-oxybate sodium intake [p = 0.0023], main model in patients without oxybate sodium intake [p = 0.0023], observed cases (i.e., completers) [p = 0.0071], and MAR imputation – actual treatment group [p = 0.0148]).

Regarding the secondary endpoints:

- **PDSS**: The mean (SD) change from baseline to end of treatment in PDSS total score was -5.54 (5.31) in the pitolisant group (N=70) and -2.09 (6.47) in the placebo group (N=37), indicating a greater improvement in the pitolisant group compared with the placebo group. After analysis, the PDSS total score at the end of the double blind period, measured by the difference in LS means between pitolisant and placebo (-3.41 (1.07) [-5.52; -1.31]) shows that the difference is **statistically significant** (p=0.0015) and that pitolisant is superior to placebo for the daytime sleepiness associated with narcolepsy. The rate of responder (i.e. patients with a change from baseline to end of treatment of at least 3 points on the PDSS) is of 64.3% [45/70] in the pitolisant group vs 40.5% [15/37] in the placebo group, which is statistically significant. Similar results were observed in the PPS with a statistically significant difference in favour of pitolisant after an 8-week treatment period on the change in PDSS total score. The main analysis results were also supported by the results of the sensitivity analyses (MNAR imputation [p=0.0021], observed cases (i.e., completers) [p=0.0020] and MAR imputation – actual treatment group [p=0.0031]).
- **UNS-CTP**: In patients with type 1 narcolepsy, the mean (SD) change from baseline to end of treatment in UNS CTP subscore was -2.83 (3.96) in the pitolisant group (N=60) and -1.27 (3.17) in the placebo group (N=28), indicating a greater improvement in the pitolisant group compared with the placebo group. There was a **statistically significant** difference in favour of pitolisant after the 8-week treatment period on the change in UNS CTP subscore in patients with type 1 narcolepsy (LS means difference (SE) [95% CI]: -1.77 (0.78) [-3.29; -0.24]; p = 0.0229). The effect of pitolisant remained significant in the PPS (p = 0.0295) and in the sensitivity analyses in the FAS (MNAR imputation [p=0.0277], completers (observed cases) imputation [p=0.0284], MAR imputation – actual treatment group [p=0.0301]).

3.3. Uncertainties and limitations about favourable effects

- **UNS**: The switch from the paediatric daytime sleepiness scale to the Ullanlinna narcolepsy scale score required further clarification and justification, given that the switch occurred when the study was nearly completed and reported outcome differences. A detailed discussion was requested about the validity, accuracy, applicability, credibility of the Ullanlinna scale score and the comparability with PDSS. A difference in scale score corresponding to a minimal clinically important difference was discussed and substantiated.
- **Cataplexy**: For medicines effective in narcolepsy, an effect is seen on both daytime sleepiness as well as cataplexy rate. Therefore the Applicant had to substantiate the clinical relevance of the effect on cataplexy in type I narcolepsy patients, as measured by the qualitative Ullanlinna narcolepsy scale score and discuss/explain the discrepancy between the paediatric and adult studies. Indeed, in the paediatric study, the effect on the cataplexy rate is almost none. In contrast in the adult studies, the cataplexy rate decreased from 9 per week to less than 4 per

week (Wakix SmPC). Further uncertainty was related to the relevance of cataplexy subscore of the Ullanlinna narcolepsy scale in paediatric patients, since the positive result on this subscore in the type 1 narcolepsy subgroup was not confirmed by the result on the secondary endpoint weekly cataplexy attacks. Indeed, the difference between pitolisant and placebo groups [2.14 (0.27) in the pitolisant group and 5.05 (0.37) in the placebo group] on the WRC during the last week of the treatment period in the double-blind phase (D49 to D56) was not significant (p=0.0540), in patients with type 1 narcolepsy in the FAS.

- **Statistical aspects**: The sponsor performed the subgroup analyses for the primary endpoint. In view of the results, the mean UNS change scores are rather consistent in each subgroup (sex, age and BMI) with those observed in the main analysis. Sex, age and/or BMI did seemingly have no influence on the UNS scores. However the evolution of UNS scores by sex, age and BMI should be interpreted with caution because of the low patient numbers in each subgroup and are only of descriptive value.

3.4. Unfavourable effects

Assessment of safety has not identified new risks in children/adolescents regarding the use of pitolisant. In the P11-06 study, from this short term 8 week study the safety profile in paediatric population appears to be comparable to the safety profile in adult population.

3.5. Uncertainties and limitations about unfavourable effects

Limited long-term safety data have been provided in the original submission and uncertainties regarding long term safety of pitolisant in paediatric patients are an issue. An open-label extension study is currently ongoing in this patient population.

3.6. Effects Table

Effects Table for pitolisant in treatment of narcolepsy

Effect	Short description	Unit	Treatment	Control	Uncertainties / Strength of evidence	References
Favourable Effects						
EDS control	Changes in Ullanlinna Narcolepsy Scale (UNS): Paediatric Daytime Sleepiness Scale (PDSS):		-6.29 [-8.51;-4.06] -5.53 [-6.82; -4.23]	-2,60[-5.25; -0.05] -2.11 ;-3.86[-0,37]	Short number of patients enrolled Short-time duration of the study p=0.0073 p=0.0015	Study report 11-06
Cataplexy control	Changes in Ullanlinna Narcolepsy Scale (UNS) –CTP:		-2.88 [3.74[-2.02]	-1.12 [-2.37; 0.13]	Short number of patients enrolled Short-time duration of the study p = 0.0229	Study report 11-06
Unfavourable Effects						

Effect	Short description	Unit	Treatment	Control	Uncertainties / Strength of evidence	References
		%	*Pitolisant*	*Placebo*	*Small number of patients Limited long-term safety*	*Study report P11-06*
AEs			34.3	31.1		
TEAEs	AEs that occurred on or after first dose of treatment up to 7 days post-last dose		30.1	35.1		
trTEAEs	AEs related to treatment		19.2	21.6		
AESIs	AEs of special interest		9.6	5.4		
SAEs	Serious AEs		0	0		
Deaths			0	0		
Headache			11	2.7		
Insomnia			5.5	2.7		

Abbreviations: AEs – Adverse Events; TEAEs - Treatment-Emergent Adverse Events; trTEAEs – treatment-related TEAEs; AESIs - Adverse Events of Special Interest; SAEs – Serious Adverse Events

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

The UNS total score at the end of the double blind period shows that the difference is statistically significant (p=0.0073) and that pitolisant is superior to placebo for the primary efficacy outcome measure.

The PDSS total score at the end of the double blind period indicates a greater improvement in the pitolisant group compared with the placebo group which was statistically significant (p=0.0015) showing that pitolisant is superior to placebo the secondary efficacy outcome measure. The rate of responder (i.e. patients with a change from baseline to end of treatment of at least 3 points on the PDSS) is of 64.3% [45/70] in the pitolisant group vs 40.5% [15/37] in the placebo group, which is statistically significant.

In patients with type 1 narcolepsy, the change in UNS-CTP subscore in patients with type 1 narcolepsy shows a statistically significant difference in favour of pitolisant at the end of the double blind period (p = 0.0229).

The concerns related to the choice and validity of the primary endpoint UNS have been solved and the effect of pitolisant on cataplexy in paediatrics have been described.

Indeed, the switch from the paediatric daytime sleepiness scale to the Ullanlinna narcolepsy scale score have been clarified and justified. Moreover a detailed discussion has been provided about the validity, accuracy, applicability, credibility of the Ullanlinna scale score and the comparability with PDSS. A difference in scale score corresponding to a minimal clinically important difference has also been discussed and substantiated as well as the validation of this scale in the paediatric population.

Regarding cataplexy, the Applicant has substantiated the clinical relevance of the effect on cataplexy in type I narcolepsy patients, as measured by the qualitative Ullanlinna narcolepsy scale score and discussed the discrepancy between the paediatric and adult studies.

This assessment of safety has not identified new risks in children/adolescents regarding the use of pitolisant. At this stage, the safety profile for pitolisant seems comparable between the adult and paediatric population.

3.7.2. Balance of benefits and risks

The overall benefit/risk balance is considered positive in the paediatric population.

3.8. Conclusions

The overall B/R of Wakix in the paediatric population is considered positive.

Outcome

Based on the review of the submitted data, the CHMP considers the following variation acceptable and therefore recommends the variation to the terms of the Marketing Authorisation, concerning the following change:

Variation accepted		**Type**	**Annexes affected**
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I and IIIB

Extension of indication to include treatment of narcolepsy with or without cataplexy in adolescents and children from the age of 6 years, based on results from Study P11-06; an ongoing phase III, double-blind, multicentre, randomized, placebo-controlled trial undertaken to evaluate safety and efficacy of pitolisant in children from 6 to less than 18 years with narcolepsy with/without cataplexy. As a consequence, sections 4.1, 4.2, 4.4, 4.8, 5.1 and 5.2 of the SmPC are updated. The Package Leaflet is updated in accordance.
Version 7.0 of the RMP has also been submitted.

The variation leads to amendments to the Summary of Product Characteristics and Package Leaflet and to the Risk Management Plan (RMP).

Amendments to the marketing authorisation

In view of the data submitted with the variation, amendments to Annex(es) I and IIIB and to the Risk Management Plan are recommended.

Paediatric data

Furthermore, the CHMP reviewed the available paediatric data of studies subject to the agreed Paediatric Investigation Plan P/0057/2021 and the results of these studies are reflected in the Summary of Product Characteristics (SmPC) and, as appropriate, the Package Leaflet.

4. EPAR changes

The EPAR will be updated following Commission Decision for this variation. In particular the EPAR module 8 "*steps after the authorisation*" will be updated as follows:

Scope

Extension of indication to include treatment of narcolepsy with or without cataplexy in adolescents and children from the age of 6 years, based on results from Study P11-06; an ongoing phase III, double-blind, multicentre, randomized, placebo-controlled trial undertaken to evaluate safety and efficacy of pitolisant in children from 6 to less than 18 years with narcolepsy with/without cataplexy. As a consequence, sections 4.1, 4.2, 4.4, 4.8, 5.1 and 5.2 of the SmPC are updated. The Package Leaflet is updated in accordance.
Version 7.0 of the RMP has also been submitted.

Summary

Please refer to Scientific Discussion 'Wakix-H-C-2616-II-30.