Safety and efficacy of pitolisant in children aged 6 years or older with narcolepsy with or without cataplexy: a double-blind, randomised, placebo-controlled trial

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Summary

Background Narcolepsy is a life-long disorder characterised by excessive daytime sleepiness and cataplexy, often arising in childhood or adolescence. Pitolisant, a selective histamine H3 receptor inverse agonist, has been approved in Europe and USA for adults with narcolepsy with or without cataplexy, with a favourable safety profile. This phase 3 study aimed to assess the safety and efficacy of pitolisant in children with narcolepsy with or without cataplexy.

Methods For this double-blind, randomised, placebo-controlled, multisite study, we recruited patients aged 6–17 years with narcolepsy with or without cataplexy in 11 sleep centres in five countries (Italy, France, Netherlands, Russia, and Finland). Participants were required to have a Pediatric Daytime Sleepiness Scale score of 15 or greater and to have not received psychostimulants for at least 14 days before enrolment; participants who needed anticataplectics (including sodium oxybate) were required to have been on a stable dose for at least 1 month. Participants were randomly assigned to treatment with pitolisant or placebo in a 2:1 ratio at the end of screening. Randomisation was stratified by study centre and treatment was allocated using an interactive web response system. After a 4-week screening period including a 2-week baseline period, patients entered in a 4-week individual up-titration scheme from 5 mg a day to a maximum of 40 mg a day of pitolisant or placebo; treatment was administered at a stable dose for 4 weeks, followed by a 1-week placebo period. For the primary analysis, we assessed pitolisant versus placebo using change in the Ullanlinna Narcolepsy Scale (UNS) total score from baseline to the end of double-blind period in the full analysis set, defined as all randomly allocated patients who received at least one dose of treatment and who had at least one baseline UNS value. A decrease in the UNS total score reflects a reduction in both excessive daytime sleepiness and cataplexy. All adverse events were assessed in the safety population, defined as all participants who took at least one dose of study medication. An open-label follow-up is ongoing. This study is registered at ClinicalTrials.gov, NCT02611687.

Findings Between June 6, 2016, and April 3, 2021, we screened 115 participants and 110 were randomly assigned (mean age 12·9 [SD 3·0] years, 61 [55%] male, and 90 [82%] with cataplexy; 72 assigned to pitolisant and 38 to placebo); 107 (70 receiving pitolisant and 37 receiving placebo) completed the double-blind period. The mean adjusted difference in UNS total score from baseline to the end of the double-blind period was –6·3 (SE 1·1) in the pitolisant group and –2·6 (1·4) in the placebo group (least squares mean difference –3·7; 95% CI –6·4 to –1·0, p=0·007). Treatment-emergent adverse events were reported in 22 (31%) of 72 patients in the pitolisant group and 13 (34%) of 38 patients in the placebo group. The most frequently reported adverse events (affecting ≥5% of patients) in either group were headache (14 [19%] in the pitolisant group and three [8%] in the placebo group) and insomnia (five [7%] in the pitolisant group and one [3%] in the placebo group).

Interpretation Pitolisant treatment resulted in an improvement in narcolepsy symptoms in children, although the UNS was not validated for use in children with narcolepsy when our study began. The safety profile was similar to that reported in adults but further studies are needed to confirm long-term safety.

Funding Bioprojet.

Introduction

Narcolepsy is a rare neurological disorder commonly starting in childhood and adolescence, with a peak of onset at the age of approximately 15 years.[1] The current International Classification of Sleep disorders (ICSD-3) distinguishes two types of narcolepsy: type 1 and type 2.[2] Narcolepsy type 1, formerly named narcolepsy with cataplexy, is characterised by a pentad of symptoms (excessive daytime sleepiness, cataplexy, sleep paralysis, hypnagogic and hypnopompic hallucinations, and disrupted nocturnal sleep) and by low or undetectable CSF hypocretin-1 concentrations. Narcolepsy type 2 is currently less well defined but shares most clinical features with narcolepsy type 1, except cataplexy, and is associated

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Research in context

Evidence before this study

The efficacy and safety of pitolisant for the treatment of excessive daytime sleepiness and cataplexy has been shown in two randomised, placebo-controlled clinical trials in adults with narcolepsy. The safety and tolerability of pitolisant in adults has been established by its use as an approved medication in Europe since 2016 and in the USA since 2019. We searched PubMed for articles published up to Dec 20, 2022, using the following search terms: "pitolisant" AND "narcolepsy" AND "(pediatric or children or child or adolescent)". One article focused on pharmacokinetics of pitolisant in paediatric narcolepsy, but no randomised, placebo-controlled trials had tested the efficacy or safety of pitolisant for the treatment of narcolepsy in children and adolescents. A few review articles reported pitolisant as a potential treatment but noted that no evidence-based data existed regarding efficacy or safety in children and adolescents; one case series has been published regarding pitolisant in the treatment of paediatric narcolepsy, and the report indicated that pitolisant was efficacious, with a safety profile consistent with studies in adults.

Added value of this study

To our knowledge, this is the first randomised, placebo-controlled trial of the safety and efficacy of pitolisant for the treatment of excessive daytime sleepiness and cataplexy in children and adolescents with narcolepsy.

Implications of all the available evidence

Before 2023, two drugs, sodium oxybate and low-sodium oxybate, were approved by the US Food and Drug Administration for the treatment of excessive daytime sleepiness and cataplexy in children with narcolepsy, a life-long, disabling disorder; however, only sodium oxybate was approved by the European Medicines Agency (EMA). On Jan 26, 2023, the EMA approved pitolisant for adolescents and children from the age of 6 years for the treatment of narcolepsy with or without cataplexy. Our prospective controlled study shows the safety of pitolisant and its efficacy in treating narcolepsy symptoms.

with normal or intermediate CSF hypocretin-1 concentrations.

Narcolepsy is currently treated with lifestyle advice and symptomatic pharmacological treatment aiming to alleviate symptoms and improve daily functioning and the disease burden.[3] Recent European guidelines recommend modafinil, methylphenidate, sodium oxybate, amphetamine, or pitolisant as first line monotherapy to manage narcolepsy symptoms in children,[4] whereas US guidelines recommend only modafinil and sodium oxybate in this population.[5] However, with the exception of sodium oxybate and low-sodium oxybate, these drugs are used off-label in most countries in children and adolescents with narcolepsy. Only sodium oxybate has been studied, in controlled clinical trials, to assess its safety and efficacy in children and adolescents who have narcolepsy with cataplexy.[6,7] More studies and approved treatments are needed for the management of narcolepsy in children and adolescents.

Pitolisant is a selective antagonist and inverse agonist of the histamine H3 receptor that promotes wakefulness in patients with narcolepsy.[8] In adults with narcolepsy with or without cataplexy, pitolisant has shown good safety and efficacy in reducing excessive daytime sleepiness and cataplexy,[9,10] and the drug obtained marketing authorisation in adults from the European Medicines Agency (EMA) in 2016 and the US Food and Drug Administration (FDA) in 2019, and on Jan 26, 2023, in adolescents and children from the age of 6 years for the treatment of narcolepsy with or without cataplexy from EMA. A pharmacokinetics study showed that pitolisant doses up to 20 mg a day (in children with body weight <40 kg) or 40 mg a day (in children with body weight ≥40 kg) are appropriate for further evaluation in paediatric patients.[11] The off-label use of pitolisant for the treatment of narcolepsy in children and adolescents has been reported in one case series, with favourable outcome (assessed clinically by interview and questionnaires) on excessive daytime sleepiness and cataplexy similar in adults.[12]

The objective of this phase 3 study was to assess the safety and efficacy of pitolisant in children and adolescents with narcolepsy with or without cataplexy.

Methods

Study design and participants

We did a double-blind, randomised, placebo-controlled, multisite study to evaluate the safety and efficacy of pitolisant in patients aged 6–17 years. Patients were recruited from 11 sleep centres with sleep medicine specialists in five countries (Italy, France, Netherlands, Russia, and Finland). The study comprised a 28-day screening period that included a 2-week baseline period, followed by an 8-week double-blind period (treatment with pitolisant or placebo) and a 1-week single-blinded (investigator aware but patient unaware) washout period. Eight face-to-face visits were planned: 4 weeks before randomisation (week –4; start of screening period); 2 weeks before randomisation (week –2; start of baseline period); week 0 (randomisation); week 3; week 4 (end of titration period); week 7; week 8 (end of double-blind treatment); and week 9 (end of washout period; appendix pp 10–11). After week 9, participants were able to enter a prolonged open-label period with pitolisant until the age of 18 years, the results of which will be described elsewhere. The protocol was approved

See Online for appendix

by either an independent ethics committee or an institutional review board at each site. Participants and their guardians provided written informed consent before enrolment. The study was done in accordance with the International Conference on Harmonisation Guidelines for Good Clinical Practice and the Declaration of Helsinki.

We planned to include 108 patients, balanced (ie, at least 40% participants per category) for age (6–11 years and 12–17 years), and sex. Individuals met ICSD-3 criteria for narcolepsy type 1 (ie, narcolepsy with cataplexy) or narcolepsy type 2 (narcolepsy without cataplexy).[2] Diagnosis was confirmed with polysomnography and Multiple Sleep Latency Test results that had been obtained within the past 12 months; if these tests has not been done in the past 12 months, they were repeated. Patients had to have a Pediatric Daytime Sleepiness Scale (PDSS)[13] score of 15 or higher during the baseline period (the mean of the scores 2 weeks before randomisation and at randomisation), and to be free of non-authorised medications, in particular psychostimulant treatments from 2 weeks before randomisation. Patients were allowed to continue their anticataplectic drugs (including sodium oxybate) if they were at a stable dosage for at least 4 weeks before randomisation (ie, from week –4 to week 0) and maintained at a stable dosage throughout the study. The previous use of psychostimulants for the treatment of excessive daytime sleepiness should have been discontinued 2 weeks before randomisation. All prohibited treatments should have been stopped 2 weeks before randomisation. Patients not taking prohibited medications could be randomly assigned two weeks after entering the study.

Randomisation and masking

Patients were randomly assigned to pitolisant or placebo (2:1) at the end of the screening period. Randomisation was stratified by study centre and treatment was allocated using an interactive web response system. A randomisation list was generated and remained confidential until after database lock on Nov 15, 2021. Participants, investigators, site personnel, and sponsor-authorised personnel were unaware of treatment allocation. In the event of a medical emergency, investigators were permitted to initiate the unmasking process but no unmasking events occurred in this study. The investigational medicinal product was developed as pitolisant hydrochloride 5 mg and 20 mg; both of these and placebo were provided in film-coated, oral-administration tablets. Packaging and treatment boxes were identical in appearance for the pitolisant and placebo groups.

Procedures

Study treatment was to be taken every day in the morning before breakfast. Patients started pitolisant or placebo with an escalating doses scheme in the first 4 weeks of the double-blind period (week 1, 5 mg a day; week 2, 10 mg a day; in week 3, the dose could be increased to 20 mg a day, maintained at the same level, or reduced to 5 mg a day, depending on investigator's assessment of efficacy and tolerability; in week 4, the dose could be increased up to 40 mg a day, maintained, or reduced). Treatment dosage at 40 mg a day was not allowed for patients with a weight of less than 40 kg. During week 5 to week 8, the dose was maintained at the same level or reduced, depending on the investigator's judgment. At the end of double-blind treatment (week 8), all patients received placebo for the 1-week washout period. At each visit, the investigator and the pharmacist controlled dispensation of the study treatment and the number of tablets of each medication (taken, forgotten) were recorded in the electronic case report form and any mismatch was investigated. The compliance with study medication was assessed by comparing the amount of medication remaining at each study visit with the amount predicted to remain if the patient was compliant with the prescription.

Outcomes

The primary efficacy endpoint was the change in the Ullanlinna Narcolepsy Scale (UNS, an 11-item scale used to measure the intensity and frequency of symptoms of narcolepsy; scores range from 0 to 44, with higher scores indicating more severe symptoms; seven of the items assess excessive daytime sleepiness and four assess cataplexy) from baseline (the mean of the scores 2 weeks before randomisation and at randomisation) to the end of double-blind period (the mean of scores at week 7 and week 8).[14,15] This study was designed in 2012 and initially focused on excessive daytime sleepiness, using the PDSS as the primary endpoint, before the 2016 EMA approval of pitolisant for the treatment of excessive daytime sleepiness and cataplexy in adult patients. The UNS, which assesses both excessive daytime sleepiness and cataplexy, was found to be more appropriate (appendix pp 30–33) and an amendment to ethics committees to consider UNS as the primary endpoint was approved by the EMA on June 26, 2020. We had four secondary endpoints: changes in excessive daytime sleepiness as measured by the PDSS (assessed at each face-to-face visit); the UNS cataplexy subscore, which consists of four items assessing knees unlocking, mouth opening, head nodding, and falling down symptoms when laughing, becoming glad or angry, or in exciting situations (only for patients with narcolepsy type 1);[14] the average number of cataplexy episodes per week (weekly rate of cataplexy [WRC], recorded in a sleep diary by the patient, parent, or teacher) between the 2 weeks before randomisation (week –2 and week –1) and the final two weeks of the double-blind phase (weeks 7 and 8, only for patients with narcolepsy type 1); and changes in wakefulness using the maintenance of wakefulness test (MWT),[16] consisting of four 30-min wake trials at week 0 and week 7. According to the amended statistical analysis plan, the primary endpoint UNS and the four secondary

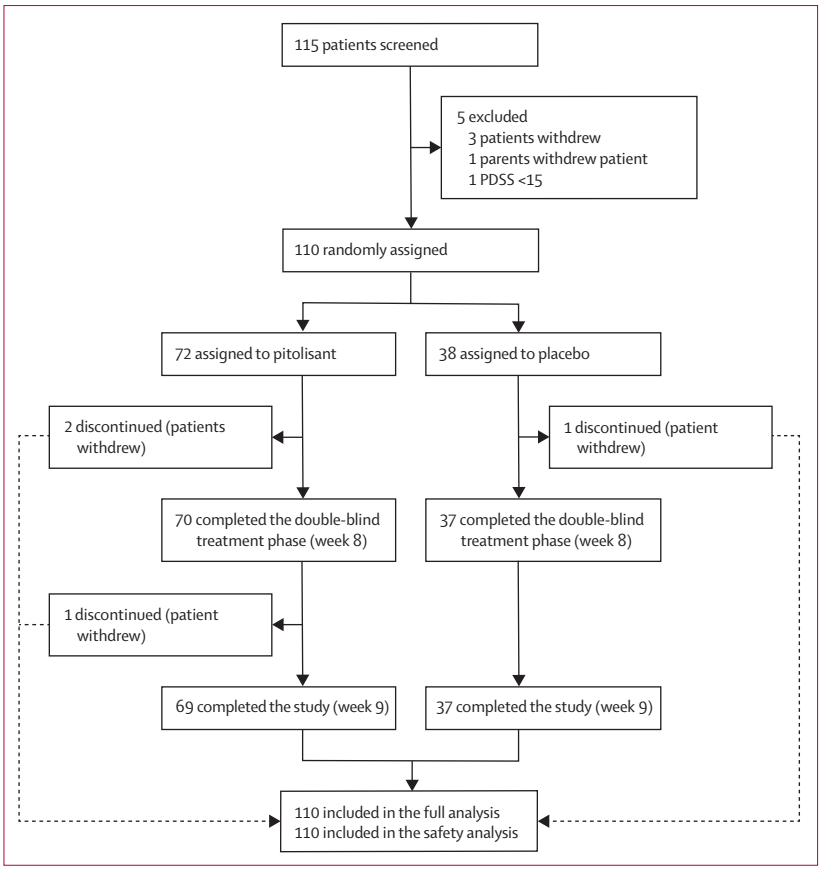

Figure 1: **Trial profile**
PDSS=Pediatric Daytime Sleepiness Scale.

	Pitolisant (n=72)	Placebo (n=38)
Sex		
Female	35 (49%)	14 (37%)
Male	37 (51%)	24 (63%)
Age, years	14 (11–16)	13 (11–15)
Age group		
<12 years	22 (31%)	13 (34%)
≥12 years	50 (69%)	25 (66%)
Type of narcolepsy		
Type 1	61 (85%)	29 (76%)
Type 2	11 (15%)	9 (24%)
Overweight	19 (26%)	7 (18%)
Obese	23 (32%)	13 (34%)
Narcolepsy duration since confirmed diagnosis, years	0 (0–3)	0 (0–3)
Multiple Sleep Latency Test at baseline	3·5 (1·7–6·1)	3·6 (1·8–6·0)
Ullanlinna Narcolepsy Scale–total score	25·0 (17·3–31·0)	24·5 (16·0–30·5)
Pediatric Daytime Sleepiness Scale	19·8 (17·3–22·5)	19·3 (17·0–22·0)
Ullanlinna Narcolepsy Scale–cataplexy subscore*	9·5 (6·5–11·5)	9·5 (6·5–11·5)
Weekly rate of cataplexy	8·63 (17·73)	13·44 (26·92)

Data are n (%), median (IQR), and mean (SD). No information on race or ethnic background were collected.
*Participants with type 1 narcolepsy only.

Table 1: **Baseline characteristics**

endpoints were analysed in a fixed sequence to preserve type 1 multiplicity error: UNS, PDSS, UNS cataplexy subscore, WRC, and MWT. The following prespecified endpoints were exploratory: clinical global impression of change both in excessive daytime sleepiness and cataplexy, Child and Adolescent Sleepiness Scale and Patient Global Opinion of the effect of treatment at each clinical visit. We report here the exploratory endpoints that we consider are most clinically relevant, and our other exploratory endpoints (UNS excessive daytime sleepiness subscore, Clinical Global Impression of Severity both in excessive daytime sleepiness and cataplexy, and test of everyday attention for children) will be reported separately.

Safety was assessed by the incidence of treatment-emergent adverse events, safety laboratory assessments, vital sign data, electrocardiogram (ECG) results, physical examinations, mood appraisal (Childhood Depression Inventory [CDI][17] evaluated at 2 weeks before randomisation, week 3, week 7, and week 9, and Columbia-Suicide Severity Rating Scale [C-SSRS][18] evaluated at each visit), and a withdrawal symptoms questionnaire as defined in DSM-IV (during a phone call 3–4 days after the week 8 visit and at week 9). An independent safety board adjudicated blinded adverse events.

Statistical analysis

The statistical analysis plan is provided in the appendix (pp 6–29). This plan was locked before the statistical analysis and breaking of the randomisation code.

All efficacy analyses were performed in the full analysis set (all randomly assigned patients who received at least one dose of study treatment and who had at least one baseline value of the UNS) and, for sensitivity purposes, in the per-protocol set (completers, all patients in the full analysis set without any major protocol deviation and having one UNS score at week 7 or week 8, appendix pp 21–22). All safety analyses were done by treatment group in the safety set (all patients who received at least one treatment dose).

For all endpoints, the effect of pitolisant compared with placebo was assessed by adjusting for baseline score and centre as random factos (mixed analysis of covariance and missing at random [MAR] multiple imputation process); results are provided as least squares means with confidence interval and p values. In the main analysis and sensitivity analyses, we compared MAR with non-missing at random (NMAR) options, fixed or random centre factor, and interaction with sodium oxybate (appendix pp 22–28). We controlled the type 1 error multiplicity through a fixed-sequence strategy[19] defined by an ordered list of the primary and secondary endpoints (UNS, PDSS, UNS cataplexy subscore, WRC , and MWT), moving to the following endpoint if the two-sided p value for the difference was less than 0·05. The WRC was analysed by a negative binomial regression and a proportional hazard cox

regression was used to compare time to sleep onset measured by the MWT.

This study originally considered the PDSS as the primary endpoint, but the primary endpoint was changed to the UNS to assess both excessive daytime sleepiness and cataplexy; this necessitated a new sample size calculation and revision of our recruitment target, from 96 patients. Assuming a baseline-final Pearson correlation coefficient of r=0·4 with a randomisation ratio of 2:1, a minimum clinically relevant standardised mean difference of 0·5 on the UNS would be detected at a 0·05 two-sided confidence level with a power of 0·85 with a sample size of at least 72 patients and 36 patients for the tested drug and control groups, respectively; thus, our recruitment target was revised to a total of 108 patients.

All statistical analyses were done using SAS software (version 9.4). This study is registered at ClinicalTrials.gov, NCT02611687.

Role of the funding source

The funder of the study (Bioprojet Pharma) had a role in study design, data collection, data analysis, data interpretation, and writing of the report.

Results

Enrolment began on June 6, 2016, and was completed on April 3, 2021. 115 patients were screened, 110 patients were enrolled and randomly assigned, and 107 (97%) completed the 8-week double-blind period (figure 1). Three patients (two in the pitolisant group and one in the placebo group) withdrew consent and discontinued from the study during the double-blind period and one patient in the pitolisant group discontinued during the 1-week single-blind washout period. Participants had a mean age of 12·9 (SD 3·0) years, 61 (55%) were male patients, 26 (24%) were overweight, and 36 (33%) were obese (table 1). 72 patients were assigned to pitolisant and 38 to placebo, and baseline characteristics were similar between the pitolisant and placebo groups. The majority of patients (90 [82%]) had type 1 narcolepsy and 20 patients (18%) had type 2 narcolepsy. 38 (35%) patients had previous treatment for narcolepsy: 20 (18%) with stimulants (eg, modafinil, methylphenidate), 17 (15%) with sodium oxybate, and 11 (10%) with antidepressant anticataplectics (eg, imipramine, clomipramine, venlafaxine). At randomisation, 11 patients were taking sodium oxybate (nine [13%] in the pitolisant group and two [5%] in the placebo group); no patient was being treated with antidepressant anticataplectics. Overall, 42 (58%) patients were treated with pitolisant 40 mg per day (ie, seven [32%] aged <12 years and 35 [70%] aged ≥12 years) and 17 (24%) were treated with pitolisant 20 mg per day (ie, ten [45%] aged <12 years and seven [14%] aged ≥12 years). Median treatment compliance was 100% (IQR 99–100) in both the full analysis set and the safety set. The mean UNS total score for all patients was 24·30 (SD 8·23) and the mean PDSS score was 20·10 (3·57).

The UNS total mean score of the adjusted difference from baseline to the end of treatment was –6·3 (SE 1·1) in the pitolisant group and –2·6 (SE 1·4) in the placebo group in the full analysis set, with a larger decrease in the pitolisant group (difference –3·7 [–6·4 to –1·0]; p=0·007;

	Pitolisant (n=72)			Placebo (n=38)			
	Baseline (mean [SD])	Week 8 (mean [SD])	Change (adjusted least squares mean difference [SE])	Baseline (mean [SD])	Week 8 (mean [SD])	Change (adjusted least squares mean difference [SE])	Treatment effect (adjusted least squares mean difference [95% CI]; p value)
Primary endpoint							
UNS	24·6 (7·8)	18·2 (8·1)*	–6·3 (1·1)	23·7 (9·1)	21·8 (9·3)†	–2·6 (1·4)	–3·7 (–6·4 to –1·0); p=0·007
Secondary endpoints							
PDSS	20·2 (3·6)	14·6 (5·4)*	–5·5 (0·7)	20·0 (3·5)	17·9 (5·6)†	–2·1 (0·9)	–3·4 (–5·5 to –1·3); p=0·002
UNS-CTP‡	8·9 (3·9)	6·0 (4·0)	–2·9 (0·4)	9·0 (4·3)	8·1 (4·6)	–1·1 (0·6)	–1·8 (–3·3 to –0·2); p=0·023
WRC‡	8·6 (17·7)	5·4 (16·5)	..	13·4 (26·9)	10·7 (18·0)	..	0·4 (0·2 to 1·0); p=0·05‡
MWT	10·1 (7·2)§	11·5 (9·1)¶	1·4 (7·2)	10·6 (8·3)	10·2 (8·7)	–0·4 (6·4)	0·8 (0·7 to 0·9)
Exploratory endpoints							
CGI-C EDS‖	..	3·1 (1·0)	..	..	3·5 (1·0)	..	–0·4 (0·0 to 0·9); p=0·05
CGI-C CTP‖	..	3·3 (1·0)	..	..	3·6 (0·9)	..	0·2 (–0·2 to 0·7); p=0·311
PGO**	..	49 (71%)	..	..	16 (43·1%)	..	27·7 (8·6 to 47); p=0·005
CASS	16·3 (3·7)	12·4 (4·4)	–3·7 (0·7)	16·1 (4·0)	14·2 (5·2)†	–1·8 (0·90)	–1·9 (–3·6 to –0·2); p=0·031

Data are mean (SD), mean change (least squares estimate of the mean change [SE]), least squares mean difference between treatment groups (95% CI), and p value. UNS=Ullanlinna Narcolespy Scale. UNS-CTP=Ullanlinna Narcolepsy Scale-cataplexy. PDSS=Pediatric Daytime Sleepiness Scale. CASS=Child and Adolescent Sleepiness Scale. WRC=weekly rate of cataplexy. MWT=maintenance of wakefulness test. CGI-C=clinical global impression of change (score from 0 [much better] to 5 [much worse]). PGO=patient global opinion. *Two values missing. †One value missing. ‡Tested on patients with narcolepsy type 1 (61 patients in the pitolisant group and 29 in the placebo group), negative binomial regression, treatment effect for WRC provided as rate ratio with 95% CIs. §Three values missing. ¶Four values missing. ‖CGI-C EDS and CGI-C CTP were CGI Change (from baseline from [1 much better] to 6 [much worse]) at week 8. PGO is a score (from 3 [marked effect] to –2 [worse effect]) done only at week 8, measuring change without score at baseline. **Measured at the end of the treatment (count of patients with a perception of improvement, %).

Table 2: **Primary, secondary, and exploratory results in the full analysis set**

table 2, figure 2). Similar results were found irrespective of the analysis set (–4·0 [–7·0 to –1·0]; p=0·01 for the per-protocol set and –3·8 [–6·5 to –1·1]; p=0·007 for completers), and all the listed sensitivity analyses (p<0·01; appendix pp 21–22). The PDSS adjusted mean difference from baseline to the end of the double-blind period showed a greater decrease in the pitolisant group than in the placebo group (table 2, figure 3). Similar results were found in the per-protocol set, and other sensitivity analyses listed in the methods (appendix pp 22–28). In patients with narcolepsy type 1, the UNS cataplexy subscore mean difference from baseline to the end of the double-blind period was greater in the pitolisant group than in the placebo group (table 2; appendix p 2). For the least squares mean WRC during the last week of treatment in the patients with narcolepsy type 1, the pitolisant to placebo rate ratio was 0·4 (95% CI 0·2; 1·0, p=0·05); therefore, according to our pre-specified fixed sequence analysis, no further analyses of significance were to be considered. Among the exploratory endpoints, we observed evidence of a potential benefit with pitolisant for Child and Adolescent Sleepiness Scale and Patient Global Opinion scores but not for clinical global impressions of change for excessive daytime sleepiness or cataplexy (table 2; appendix p 35).

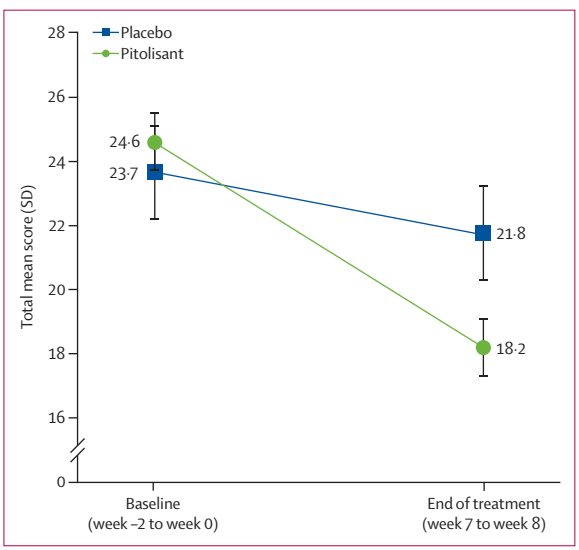

Figure 2: **Ullanlinna Narcolepsy Scale total score**
Change in the mean Ullanlinna Narcolepsy Scale total score from baseline to the end of treatment in the full analysis set.

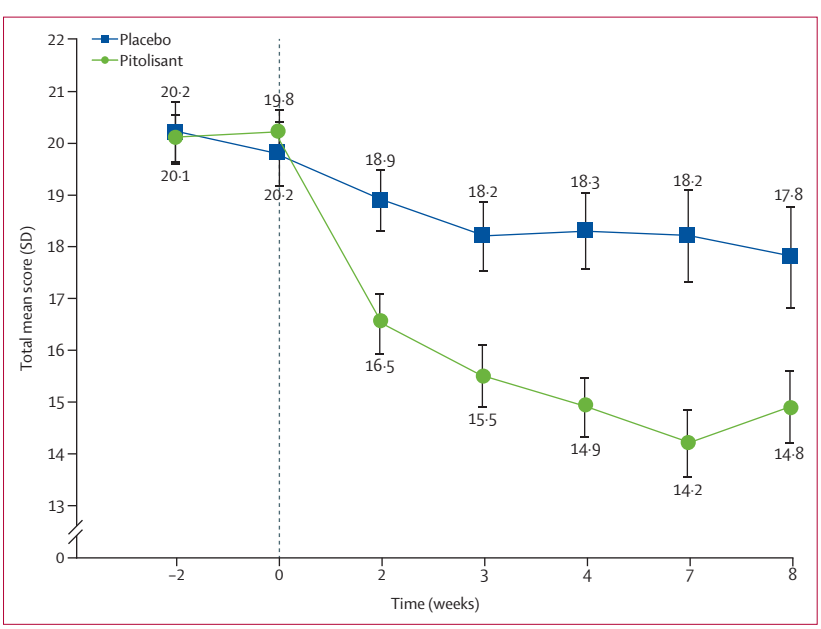

Figure 3: **Pediatric Daytime Sleepiness Scale total score**
Pediatric Daytime Sleepiness Scale was completed at each visit in the double-blind phase.

89 treatment-emergent adverse events were reported in 35 (32%) of 110 patients. The proportion of patients with at least one treatment-emergent adverse event was similar in the pitolisant group (22 patients [31%]) and the placebo group (13 patients [34%]; table 3). The most frequently reported (≥5% of patients overall) treatment-emergent adverse events were headache and insomnia. Three treatment-emergent adverse events were severe. These events were all reported by two patients in the pitolisant group: pyrexia and headache in a 16-year-old female patient with obesity and type 1 narcolepsy receiving 20 mg (the patient recovered and their dose was increased to 40 mg without recurrence) and persistent insomnia in a female patient with type 1 narcolepsy receiving 20 mg pitolisant. All other treatment-emergent adverse events were mild (62 [70%] of 89) or moderate (24 [27%] of 89). A total of 47 treatment-related treatment-emergent adverse events were reported in 22 patients (20%) with similar frequencies in the pitolisant group (14 [19%] of 72) and the placebo group (eight [21%] of 38). The most frequently reported treatment-related treatment-emergent adverse events in the pitolisant group (≥2% of patients) were headache in eight (11%), insomnia in four (6%), and hypertension in two (3%) participants. Two patients had mild hypertension that recovered without sequelae: a female patient aged 17 years who was overweight and receiving 10 mg pitolisant daily had an transient increase (systolic blood pressure–diastolic blood pressure of 122–78 mm Hg) for 1 day between the week 2 and week 3 visits from already abnormal baseline values (122–68 mm Hg); a male patient aged 16 years with healthy weight had a transient increase (145–90 mm Hg) after 6 days of placebo between the week 8 and week 9 visit, improving 3 days later (131–86 mm Hg). No antihypertensive medications were prescribed. There were no deaths, no serious treatment-emergent adverse events, and no discontinuations of pitolisant related to treatment-emergent adverse events.

We found no clinically relevant changes in laboratory values, vital signs (systolic and diastolic blood pressure, heart rate, and BMI), and physical examinations (appendix pp 36–38). For the majority of patients, no notable changes were found in the ECG results; only one

patient had an abnormal ECG, in the pitolisant group at week 4 (heart rate decreased from 87 beats per minute at week 2 to 59 beats per minute at week 4, without concomitant medication intake). The percentage of patients reporting none or minimal depression increased from baseline to week 7 in both the pitolisant and the placebo groups. No patients had severe depression according to the CDI, for each visit; however, three patients (one in the pitolisant group at week 7, one in the placebo group at week 3, and one in the placebo group at week 7) were considered to be at suicide risk but had not engaged any suicidal behaviour or ideation, according to the C-SSRS, without any suicide risk at the following study visits, without antidepressant treatment (appendix p 38). According to the DSM IV, the definition of amphetamine-like withdrawal syndrome was met by seven (10%) of the 72 participants in the pitolisant group and two (5%) of the 38 participants the placebo group during a phone call 3–4 days after the week 8 visit and by 12 (17%) participants in the pitolisant group and three (8%) participants the placebo group at the face-to-face week 9 visit.

Discussion

In this phase 3, placebo-controlled, double-blind, multicentre study, pitolisant at 5 mg to 40 mg a day showed clinically meaningful improvements in narcolepsy symptoms in children aged 6 to 17 years with narcolepsy with or without cataplexy. In patients with narcolepsy with cataplexy, pitolisant also reduced the frequency of cataplexy.

This is the first study assessing safety and efficacy of pitolisant in paediatric narcolepsy, but previous clinical trials in adults with narcolepsy with or without cataplexy have shown positive results in terms of excessive daytime sleepiness and cataplexy.[9,10] The HARMONY I study showed a mean reduction of 3 points on the Epworth Sleepiness Scale over placebo,[9] and the HARMONY CTP trial showed a reduction by half of the WRC compared with placebo.[10] We also reported the long-term safety and efficacy of pitolisant on excessive daytime sleepiness, cataplexy, hallucinations, and sleep paralysis in an open-label pragmatic study in adult patients with narcolepsy.[20]

In this multicentric study including patients with narcolepsy with severe excessive daytime sleepiness (ie, PDSS >15) with (82%) and without (18%) cataplexy, the efficacy of pitolisant compared with placebo was shown on narcolepsy symptoms with the significant changes in UNS total score and PDSS after an 8-week treatment period in children with narcolepsy in both the full analysis set and the per-protocol set. An objective measure of wakefulness, the MWT sleep latency, increased in the pitolisant group compared with the placebo group, but the effect size was small and the results cannot be considered statistically significant given our fixed sequence strategy to control for the multiplicity of tests. In patients with narcolepsy with cataplexy, pitolisant decreased significantly the UNS cataplexy subscore after an 8-week treatment period.

	Pitolisant (n=72)	Placebo (n=38)
Treatment-emergent adverse events	60	29
Patients with ≥1 treatment-emergent adverse events	22 (31%)	13 (34%)
Treatment-emergent adverse events ≥5%, in either group		
Headache	24 events (14 patients [19%])	4 events (3 patients [8%])
Insomnia	5 events (5 patients [7%])	1 event (1 patient [3%])
Treatment-emergent adverse events of severe intensity	3* events (2 patients [3%])	0
Treatment-related treatment-emergent adverse events†	35 events (14 patients [19%])	12 events (8 patients [21%])
Treatment-emergent adverse events of special interest		
Anxiety	1 event (1 patient [1%])	1 event (1 patient [3%])
Dyspepsia	1 event (1 patient [1%])	0
Insomnia	5 events (5 patients [7%])	1 event (1 patient [3%])

Data are n events (n patients [%]). *The three events were: pyrexia and headache in one patient and insomnia in one patient. †There were no deaths, serious adverse events, or discontinuations due to treatment-emergent adverse events.

Table 3: **Treatment-emergent adverse events**

Altogether, our results on self-reported sleepiness and cataplexy via the UNS support the efficacy of pitolisant in paediatric patients with narcolepsy, consistent with a retrospective case series of four children and adolescents.[12] These results are in line with the mechanisms of action of pitolisant, which involve increasing the synthesis and release of histamine in the brain via competitive binding to presynaptic H3 autoreceptors, and also increasing the activity of other wake-promoting neurotransmitters (eg, acetylcholine, dopamine, and norepinephrine) by binding to H3 receptors on nonhistaminergic neurons, without activation of accumbal dopaminergic neurons.[8,21]

Pitolisant was well tolerated and no serious or severe treatment-related adverse reactions were reported. The most frequent adverse events with pitolisant were headache and insomnia. We recorded no severe changes in ECG (eg, QT interval prolongation) or other cardiovascular outcomes, confirming a favourable cardiovascular safety profile. Also, we did not identify any particular safety issues in patients who were taking other medications. However, in clinical practice, when the add-on of a drug with a risk of QT interval prolongation is considered in patients on stable doses of pitolisant, there is an increased risk of cardiac arrhythmias, which must always be carefully assessed. The safety profile of pitolisant was thus consistent with that observed in adult patients.[20]

Sodium oxybate is the only drug approved by the FDA and EMA to treat cataplexy and excessive daytime sleepiness in paediatric patients with narcolepsy, and

low-sodium oxybate has also been approved by the FDA in this population. Furthermore, on Jan 26, 2023, EMA approved pitolisant for adolescents and children from the age of 6 years for the treatment of narcolepsy with or without cataplexy. With our results, pitolisant might be another first-choice treatment option in the management of narcolepsy and cataplexy in children and adolescents. Once daily dosing of pitolisant might also be of advantage in the treatment of narcolepsy symptoms in paediatric patients compared with the twice nightly sodium oxybate and low-sodium oxybate regimen. Based on the favourable safety profile in people using sodium oxybate as well as pitolisant in our study and a cross-sectional study from the large cohort of Italian patients,[22] clinicians might also consider a combination of these treatments to manage complex or severe cases of paediatric narcolepsy, as already described in adults with narcolepsy.[3,4,20,22] Paediatric narcolepsy is a complex disease, still often misdiagnosed and unrecognised, which requires raising awareness outside the community of sleep specialists to improve the diagnosis, to reduce diagnostic delay, and to obtain rapid, effective, and multidisciplinary management.[23–25]

Our study has limitations. Its short duration does not address whether tolerance to pitolisant will develop with continued treatment; however, long-term safety and efficacy of pitolisant were confirmed in adult patients with narcolepsy.[20] The results of open-label use of pitolisant for up to 5 years in this paediatric population will be described elsewhere. Anticataplectic drugs (sodium oxybate) at stable dose for at least 4 weeks were allowed in this study, which might have led to underestimation of the effects of pitolisant on the frequency of cataplexy, excessive daytime sleepiness, and sleep quality. The flexible dosage and multiple visits could have affected the treatment efficacy, with less responsive patients being more likely to be titrated to the highest dose. Some participants without cataplexy at baseline, with a low frequency of cataplexy at baseline, or taking a stable dose of anticataplectic medication (sodium oxybate) were included, which might bias the analysis of the effects of pitolisant on the frequency of cataplexy. Also, the recall of cataplexy episodes can be inaccurate in young children, with episodes recorded in the diary by a parent or teacher in case of difficulty. The low numbers of participants in subgroups for age (<12 years and ≥12 years), different doses, and co-medication intake (eg, sodium oxybate) do not allow a clear assessment of the efficacy of pitolisant in these subpopulations. Based on the inclusion criteria, this trial population might not be representative of the general narcoleptic population, being the narcoleptic symptoms more severe than in a general narcoleptic population and because ethnic background was not assessed.

We included patients with type 2 narcolepsy meeting the ICSD-3 criteria (excluding clinically chronic sleep deprivation)[2] to provide a representative population of children and adolescents with narcolepsy. No analysis of excessive daytime sleepiness in the type 1 and type 2 narcolepsy subgroups was pre-specified in the initial statistical analysis plan; thus, we did not give results for the different types of narcolepsy and the study was not sufficiently powered for analysis of these subgroups. Consequently, some caution should be taken when evaluating the efficacy of pitolisant in the treatment of childhood narcolepsy without cataplexy, and further confirmations are needed. A significant effect on the frequency of cataplexy was shown in patients with type 1 narcolepsy, this analysis having been prespecified. Overall, pitolisant is generally well tolerated in children, with comparable results in those aged below or above 12 years. The UNS, the primary endpoint of this study, was not validated in children when the study began, and was not previously used as an endpoint in clinical and research narcolepsy studies, unlike the Epworth Sleepiness Scale for Children and Adolescents,[26] the PDSS,[13] or, more recently, the Pediatric Narcolepsy Severity Scale for children with narcolepsy.[27] However, an analysis of partial data from our trial showed that the UNS is a reliable and sensitive measurement tool, assessing both cataplexy and sleepiness symptoms in children with narcolepsy with a high correlation to patient-perceived status.[15] Further studies are needed to confirm the validity of the UNS in independent populations of paediatric narcolepsy.

In conclusion, in children with narcolepsy aged 6 years or older, pitolisant 5 mg to 40 mg a day showed significant efficacy in reducing excessive daytime sleepiness and cataplexy. The safety profile of pitolisant was consistent with that observed in adults and adverse events were generally mild, suggesting good benefit–risk profile in children and adolescents with narcolepsy.

Contributors

YD and GP were involved in study conceptualisation and in writing of the original draft of the manuscript. IJ, CC, JML, and JCS were involved in data curation. YD, GP, and JCS were involved in methodology and formal analysis. YD was involved in validation and supervision. GP was trial coordinator and investigator, and YD, ML, GJL, PF, and MP were trial investigators. PL was involved in statistical analyses. YD, GP, GJL, PF, and ML verified the data. All authors had full access to the data, were involved with review and editing of the manuscript, approved the final version of the manuscript, and had final responsibility for the decision to submit for publication.

Declaration of interests

YD reports grant and consultancy fees from Bioprojet, Idorsia, Avadel, Harmony Biosciences, Takeda, and Jazz Pharmaceuticals, during the conduct of the trials. GP reports grant and consultancy fees from Bioprojet, Idorsia, Takeda, Orexia, Fidia, and Jazz Pharmaceuticals. PF reports grant and consultancy fees from Bioprojet and Jazz Pharmaceuticals. ML reports consultancy fees from Bioprojet, and Jazz Pharmaceuticals. GJL reports grant and consultancy fees from Bioprojet and Jazz Pharmaceuticals. IJ, CC, JML, and JCS are employees of Bioprojet. MP and PL declare no competing interests.

Data sharing

Researchers can submit requests for individual participant data that underlie the results reported in this article, after deidentification, after the publication of study results to the sponsor; those who send a methodologically sound proposal (as judged by the sponsor) will receive data within 3 months from the initial request.

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