Pitolisant versus placebo or modafinil in patients with narcolepsy: a double-blind, randomised trial

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Summary

Background Narcolepsy is characterised by excessive daytime sleepiness (EDS) and cataplexy. Histamine neurons are crucial to maintain wakefulness. We assessed the safety and efficacy of pitolisant (previously called BF2.649), a selective histamine H3 receptor inverse agonist that activates these neurons, in patients with narcolepsy.

Methods For this double-blind, randomised, parallel-group controlled trial, we recruited patients with narcolepsy from 32 sleep disorder centres in five European countries. Patients were eligible if they were aged 18 years or older, had not taken psychostimulants for at least 14 days, and had EDS (defined as an Epworth Sleepiness Scale [ESS] score of at least 14). Using a computer-generated randomisation sequence, we randomly allocated patients to receive pitolisant, modafinil, or placebo (1:1:1). Treatment lasted 8 weeks: 3 weeks of flexible dosing according to investigator's judgment (10 mg, 20 mg, or 40 mg a day of pitolisant; 100 mg, 200 mg or 400 mg a day of modafinil) followed by 5 weeks of stable dosing. Patients took four tablets a day in a double-dummy design to ensure masking. For the primary analysis, assessed in the intention-to-treat population, we assessed the superiority of pitolisant versus placebo, and the non-inferiority of pitolisant versus modafinil. This trial is registered with ClinicalTrials.gov, number NCT01067222.

Findings Between May 26, 2009, and June 30, 2010, we screened 110 patients, 95 of whom were eligible and randomly assigned to treatment: 30 to placebo, 32 to pitolisant, and 33 to modafinil. Over the 8-week treatment period, mean ESS score reductions were –3·4 (SD 4·2) in the placebo group, –5·8 (6·2) in the pitolisant group, and –6·9 (6·2) in the modafinil group. Our primary analysis of between-group differences in mean ESS score at endpoint (adjusted for baseline) showed pitolisant to be superior to placebo (difference –3·0, 95% CI –5·6 to –0·4; p=0·024), but not non-inferior to modafinil (difference 0·12, 95% CI –2·5 to 2·7; p=0·250). We recorded 22 adverse events with pitolisant, 26 with modafinil, and ten with placebo. Six severe adverse events were treatment-related: one with pitolisant (abdominal discomfort) and five with modafinil (abdominal pain, abnormal behaviour, amphetamine-like withdrawal symptoms, lymphoadenopathy, and inner ear disorders).

Interpretation Pitolisant at doses up to 40 mg was efficacious on EDS compared with placebo and well tolerated compared with modafinil. If these findings are substantiated in further studies, pitolisant could offer a new treatment option for patients with narcolepsy.

Funding Bioprojet, France.

Introduction

Narcolepsy is a rare disabling disorder with a prevalence of about 0·05%. Narcolepsy is characterised by excessive daytime sleepiness (EDS), impaired ability to sustain attention, and abnormal REM sleep manifestations, including cataplexy, sleep paralysis, and hallucinations.[1,2] Narcolepsy is caused by loss of hypothalamic hypocretin (orexin) neurons,[3] a deficit which cannot be compensated by administration of hypocretins because they have poor bioavailability.

Available treatments are psychostimulants—eg, modafinil (or armodafinil, its R-isomer)—to treat EDS, and sodium oxybate to alleviate cataplexy and decrease EDS.[4–6] Antidepressants are also used to treat cataplexy.[7] However, a need still exists for drugs with improved safety and efficacy.

Tuberomammillary histaminergic neurons, which are crucial for maintenance of wakefulness,[8,9] seem largely, if not completely, preserved in narcolepsy,[10–12] and seem to be essential in the waking action of hypocretins.[13] Hence, we tested whether the hypocretin deficit could be circumvented by activating these neurons. Pitolisant (previously called BF2.649 and tiprolisant), an inverse agonist of the histamine H3 receptor, activates histamine release in the brain, increases wakefulness, and decreases narcolepsy episodes in hypocretin-knockout mice, and, in a small single-blinded trial, decreased EDS in narcoleptic patients.[14] We assessed the safety and efficacy of pitolisant in comparison with placebo and modafinil.

Methods

Patients and study design

We recruited patients from 32 centres in five European countries (France, Germany, Netherlands, Hungary, and Switzerland). Eligible patients were aged 18 years or older with narcolepsy with or without cataplexy[15] and with self-reported daily EDS for more than 3 months; narcolepsy was confirmed by polysomnogram, a multiple

sleep latency test done within the previous 5 years showing a mean sleep latency of 8 min or less with two or more sleep onset rapid eye movement periods, and an Epworth sleepiness scale (ESS)[16] score of 14 or more (the maximum score is 24).

Patients had no psychostimulants for 14 or more days before baseline but could remain on their anticataplectic drugs (sodium oxybate or antidepressants) at stable doses 1 month before and throughout the trial. Tricyclic antidepressants, most of which have H1-antihistamine properties, were not allowed.

Women of child-bearing potential had to use a birth control method. Exclusion criteria were the use of any investigational drug within 30 days before screening, any other disorder that could be the main cause of EDS in patients without cataplexy (eg, sleep-related breathing disorder with sleep apnoea index ≥10 per h, an apnoea or hypopnoea index of ≥15 per h, or a periodic limb movement disorder with arousal index of ≥10), a history of substance abuse, a serious cardiovascular disorder, hepatic or renal abnormalities, or a psychiatric disorder.

The study was approved by local ethics committees in each country: CPP Sud-Méditerranée III (France), Ethik Kommission bei der Landesärztekammer Hessen (Germany), Medical Research Council Ethic Committee for Clinical Pharmacology (Hungary), Leids Universitair Medisch Centrum (The Netherlands), Kantonale Ethikkommission Bern, Commission Centrale d'Ethique et de la Recherche des Hôpitaux Universitaires de Genève, and Ethikkommission des Departementes Gesundheit und Soziales (Switzerland). Patients provided written informed consent during the selection visit and before any study procedure was done. In agreement with ethics committees, no data safety monitoring board was established.

Randomisation and masking

We randomly assigned eligible patients to receive pitolisant, modafinil, or placebo (1:1:1). The randomisation sequence was computer-generated by Creapharm (Bordeaux, France) and transmitted to Lambda Plus (Gembloux, Belgium) via an interactive web response system. The investigator at each site interacted confidentially with the web response system to communicate dosage strength allocation. The two contract research organisations (CROs) had no further role in the study.

We masked treatment allocation through use of double-dummy medication. Pitolisant, modafinil, and placebo were given in sealed capsules, which were similar in appearance and taste and contained a half tablet of pitolisant 20 mg, or one tablet of pitolisant 20 mg, or one tablet of modafinil 100 mg, or lactose only (placebo capsules). Tablets containing active treatments were completed with lactose to avoid any differentiation with placebo.

The dose-escalation scheme was applied to the three types of treatment with double-blinding maintained

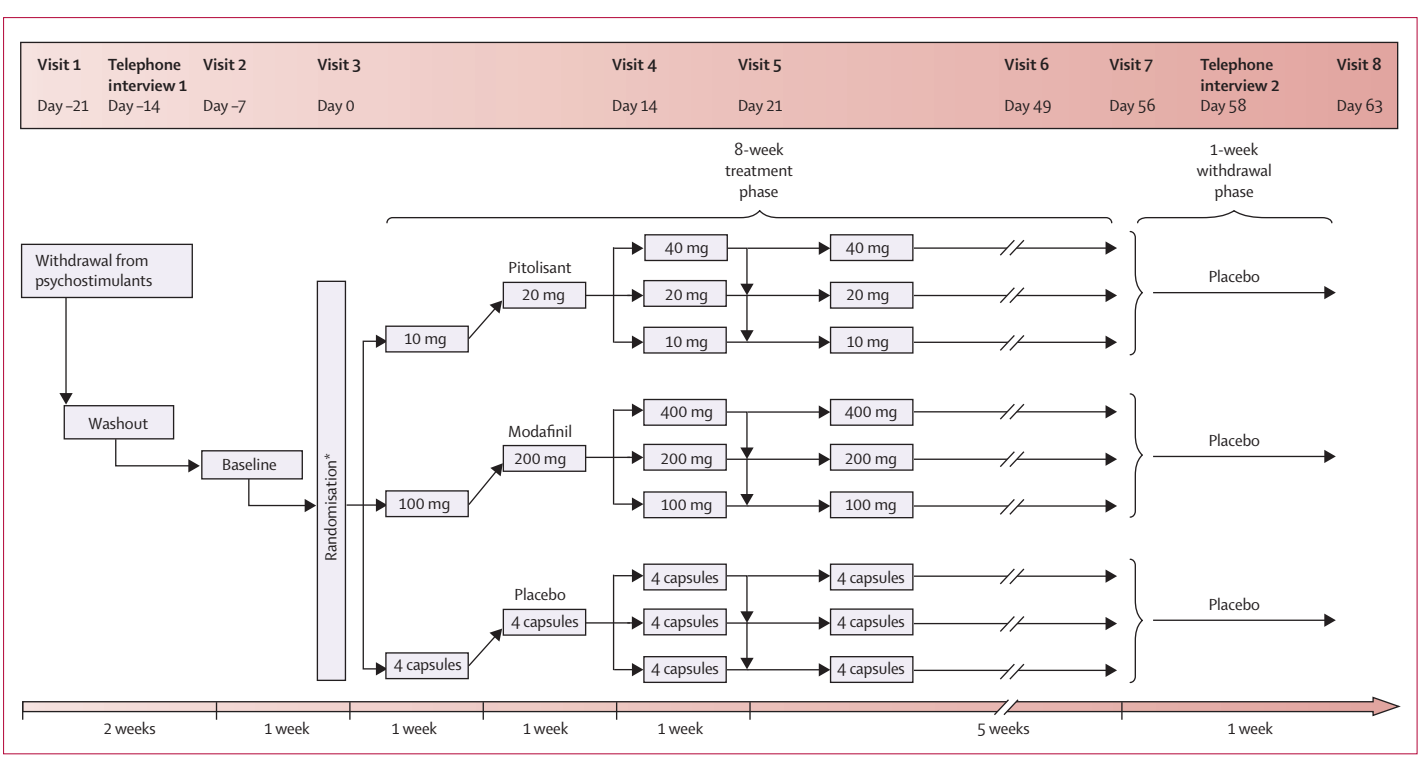

Figure1: **Trial design**

*If patients had an Epworth sleepiness scale of 14 or higher.

throughout the trial. All patients took four capsules per day whatever the treatment or dose: two before breakfast and two before lunch, no later than 1430 h to preserve night-time sleep. Patients on pitolisant or on 100 mg modafinil took all doses of drug in the morning and received two dummy capsules to take before lunch.

Procedures

After a 3 week selection period, patients meeting all selection criteria were randomly assigned to treatment groups and were instructed to start the study drug the next morning. Treatment lasted 8 weeks: 3 weeks of flexible dosing followed by 5 weeks of stable dosing. During the first 7 days, all patients took a low dose (10 mg of pitolisant or 100 mg of modafinil or placebo), then a medium dose (20 mg of pitolisant or 200 mg of modafinil or placebo) for the next 7 days (figure 1). On day 14 after randomisation, doses were adjusted for each patient on the basis of individual clinical efficacy and safety assessed by investigators; no specific recommendations were given to the investigators for this adjustment. Patients could then receive 10 mg, 20 mg, or 40 mg of pitolisant, or 100 mg, 200 mg, or 400 mg of modafinil, or placebo. On day 21, investigators could decrease the dose in the case of insufficient tolerance only. Patients continued at their assigned stable dose for an additional 5 weeks. On day 49, patients made a control visit, and treatment was stopped at day 56. Patients then received 1 week of placebo in a withdrawal phase.

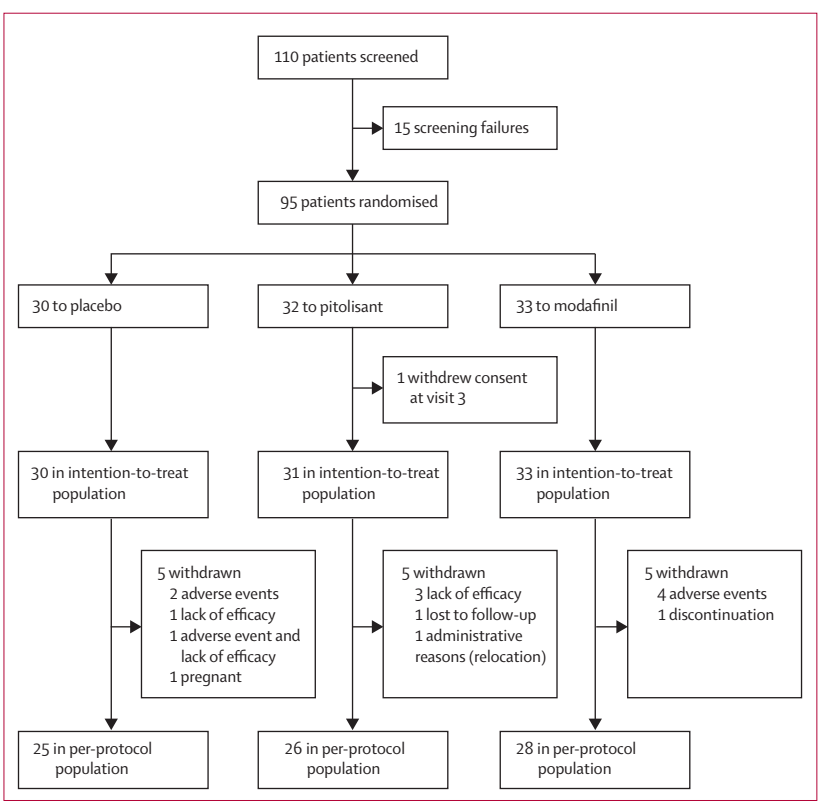

Figure 2: **Trial profile**

The primary endpoint was the difference in change in ESS scores between the pitolisant and placebo groups after the 8-week treatment period. We planned to assess the difference in ESS score change between the pitolisant and modafinil groups if there was a statistically significant difference between pitolisant and placebo. ESS is a self-administered questionnaire assessing chances of falling asleep in eight life situations (eg, watching television).[16]

Secondary efficacy endpoints were the maintenance of wakefulness test (MWT),[17] sustained attention to response task (SART),[18] modified clinical global impression of change (CGI-C) targeting EDS and cataplexy, European quality-of-life questionnaire (EQ-5D), patient's global opinion of their treatment, and symptoms of cataplexy assessed by patients' sleep diaries (recorded electronically or on paper; symptoms recorded were sleep attacks, episodes of severe sleepiness, cataplexy attacks, hypnagogic or hypnopompic hallucinations, sleep paralysis, nocturnal awakening, and nocturnal sleep time). MWT and SART were both administered in four sessions during inclusion (visit 3) and at the end of the 8-week treatment phase (visit 7). In the MWT sessions (40 min) the ability to stay awake was measured in minutes. The SART, a laboratory measure of sustained attention, comprises three error scores: the number of times a button was pressed inappropriately ("NO GO"), the number of times key pressing was missed ("GO"), and the sum of these two scores.

We recorded the occurrence of any adverse events at each visit. Additional safety measures included haematology and blood chemistry tests, vital signs, electrocardiograms, and physical examination.

We assessed the occurrence of withdrawal syndrome (as defined in DSM-4[19]—dysphoria plus three of the following symptoms: fatigue, vivid and unpleasant dreams, insomnia or hypersomnia, increased appetite, psychomotor retardation or agitation) during a telephone interview about 3 days after the end of treatment, confirmed and recorded in a face-to-face clinical interview at visit 8 (63 days after randomisation), focusing on the 1 week placebo period. The study was monitored by CROs (RPS [Boulogne-Billancourt, France], TFS [Berghem, Netherlands], Clinical Investigations [Budapest, Hungary]).

Statistical analysis

We calculated the sample size on the basis of data from previous trials,[20,21] based on the minimum clinically relevant difference on a final ESS of 3 points, ESS SD of 5, and a coefficient of correlation r (baseline ESS, final ESS) of 0·65. The first test (difference in change of ≥3 points detectable with a power ≥95%) and the second test (non-inferiority margin of 2 points and 80% as minimal power) needed a sample size of 30 patients per group.

We included patients who had at least one dose of study drug and provided at least one post-baseline value in our intention-to-treat population. Analysis in all randomly allocated patients and per-protocol population (patients attending every visit until at least visit 8, without major protocol deviation) were sensitivity analyses.

We adjusted final ESS for baseline values for assessment of the primary endpoint using a mixed linear analysis of covariance, assuming absence of treatment-baseline interaction term and accounting for random centre heterogeneity. Baseline ESS was the summary mean of pre-baseline and end of baseline values (day –7 [7 days before baseline] and day 0). The final ESS was the summary mean of values at days 49 and 56. We used a step-down approach for multiple treatment comparisons: we first tested the superiority of pitolisant over placebo, then, if shown to be superior, we planned to test the non-inferiority of pitolisant versus modafinil, based on a non-inferiority margin of 2 ESS points. This value was half the difference between modafinil and placebo in previous trials:[20,21] mean change 4·02, 95% CI 0·14–7·09.

We compared MWT and SART changes over baseline with geometric means. Other secondary endpoints were analysed descriptively. Missing data were imputed according to the last observation carried forward, with the final value calculated as the mean of the two last known values. For sensitivity purposes, we did two alternative imputations: we estimated missing data using a mixed model, without systematic imputation, by assuming hypotheses of compound symmetry and autoregressive correlation between examinations;[22] and we imputed a worst case scenario value (baseline value—ie, no change) for the final value of any patient with premature interruption of treatment.

We did two post-hoc analyses. The first was the calculation of a daily cataplexy rate in the population with cataplexy, which we defined as at least one cataplexy episode during baseline (week preceding randomisation) or study treatment period. We compared changes from baseline to the final period (between days 49 and 56) between groups using a quasi-Poisson regression model. The second post-hoc analysis was the calculation of ESS responder rates, defined as patients with a final ESS of 10 or lower, using a Poisson regression model. We used SAS (version 9.2) for all statistical analyses.

This trial is registered with ClinicalTrials.gov, number NCT01067222.

	Placebo (N=30)		Pitolisant (N=31)		Modafinil (N=33)	
	N	Value	N	Value	N	Value
Age in years	30	39·5 (30–52)	31	33·0 (21–49)	33	40·0 (25–48)
Weight in kg	30	81·0 (20·7)	31	90·9 (21·0)	33	81·0 (16·3)
Height in cm	30	168·0 (10·4)	31	173·9 (9·8)	33	171·0 (8·5)
Body-mass index (kg/m²)	30	28·2 (6·0)	31	30·4 (8·3)	33	27·7 (5·3)
Men		13 (43%)		20 (65%)		18 (55%)
Ethnic origin (white)		27 (90%)		29 (94%)		32 (97%)
Duration of narcolepsy in years	30	14·9 (8·8–24·8)	31	10·6 (7·8–17·9)	33	11·7 (5·3–19·8)
Multiple sleep latency test	18	5·4 (2)	20	3·7 (2·6)	20	4·9 (2·4)
History of cataplexy	30	24 (80%)	31	25 (81%)	33	27 (82%)
History of associated symptoms	30		31		33	
Sleep paralysis		15 (50%)		15 (48%)		22 (67%)
Hypnagogic hallucinations		19 (63%)		18 (58%)		24 (64%)
Automatic behaviour		9 (30%)		15 (48%)		16 (49%)
Bad night-time sleep		14 (47%)		18 (58%)		20 (61%)
Patients with at least one long-term course of medication within the 3 months before inclusion	30	13 (43%)	31	14 (45%)	33	16 (50%)
Patients treated with modafinil before baseline	30	13 (43%)	31	13 (42%)	33	11 (33%)
ESS score ([visit 2 + visit 3] ÷ 2)	30	18·9 (2·5)	31	17·8 (2·5)	33	18·5 (2·7)
SART-NOGO	30	8·0 (1·8)	29	9·2 (1·8)	33	8·5 (1·6)
SART-Total	30	13·6 (11·7)	30	13·6 (7·7)	33	13·8 (13·7)
MWT	30	11·5 (2·0)	31	12·5 (1·9)	33	11·6 (2·0)
Cataplexy episodes (episodes per day)	14	0·92 (0·87)	20	1·2 (1·8)	23	1·1 (1·9)
Sleep paralysis episodes (daily rate)	9	0·33 (0·35)	8	0·29 (0·42)	14	0·27 (0·27)
Hallucination episodes (daily rate)	13	0·73 (1·73)	11	0·15 (0·22)	15	0·32 (0·50)

Data are median (IQR), mean (SD), or n (%). ESS=Epworth sleepiness scale. SART=sustained attention reaction test. MWT=maintenance of wakefulness test.

Table 1: **Baseline characteristics (intention-to-treat population)**

Role of the funding source
The protocol was developed by the sponsor (C-LD, J-ML, J-CS), with guidance from a steering committee of European academic experts (YD, CB, GJL, PL, and GM). The sponsor had no role in the collection, analysis, or interpretation of data. The paper was written by the sponsor (J-CS), with revisions made by the expert panel (YD, CB, GJL, GM, and PL) and approved by all authors. All authors had full access to all data and YD made the final decision to submit the paper for publication.

Results

Between May 26, 2009, and June 30, 2010, we screened 110 patients, 95 of whom were eligible and randomly assigned to treatment: 30 to placebo, 32 to pitolisant, and 33 to modafinil (figure 2).

Of the 94 patients included in the intention-to-treat analysis, 76 (81%) had cataplexy, 42 (45%) had taken psychostimulants (mostly modafinil or methylphenidate; 13 of 30 patients in the placebo group, 13 of 31 in the pitolisant group, and 11 of 33 in the modafinil group), and 33 (35%) were using anticataplectic drugs and continued them at stable dosage during the trial; of those using anticataplectic drugs, eight (four in the placebo group, two in the pitolisant group, and two in the modafinil group) were on sodium oxybate and 25 used antidepressants. 57 (61%) patients were considered still cataplectic during the trial, reporting one or more cataplexy episode during the trial. The per-protocol population comprised 79 patients who completed the study: 25 in the placebo group, 26 in the pitolisant group, and 28 in modafinil group. Reasons for discontinuation (figure 2) and baseline characteristics (table 1) were much the same between treatment groups. Dose reductions at visit 4 or 5 occurred in none of the patients in the placebo group, two patients in the pitolisant group, and two patients in the modafinil group.

In the intention-to-treat population, patients given pitolisant had a greater ESS improvement from baseline than those given placebo (table 2). The superiority criterion of pitolisant over placebo being met, we tested the non-inferiority of pitolisant versus modafinil. Our findings showed that pitolisant was not non-inferior to modafinil (table 2). During the trial, ESS decreased at a similar rate in the pitolisant and modafinil groups (figure 3), and we saw no statistically significant between-group differences in analysis of all randomly allocated patients and the per-protocol population (data not shown). Sensitivity analyses with the alternative missing data imputation rules did not change the results (data not shown).

MWT values decreased from baseline in the placebo group but improved in the pitolisant group, and superiority of pitolisant over placebo was shown (table 2). MWT also improved from baseline in the modafinil

	Placebo			Pitolisant			Modafinil			Treatment effect (mean difference [95% CI]; p value)	
	Baseline	Final	Change over trial*	Baseline	Final	Change over trial*	Baseline	Final	Change over trial*	Pitolisant *vs* placebo (superiority test)	Pitolisant *vs* modafinil (non-inferiority test)
ESS (primary endpoint; change = final − baseline)	18·9 (2·5)	15·6 (4·3)	−3·4 (4·2)	17·8 (2·5)	12·0 (6·2)	−5·8 (6·2)	18·5 (2·7)	11·6 (6·0)	−6·9 (6·2)	−3·0 (−5·6 to −0·4); p=0·024	0·12 (−2·5 to 2·7); p=0·250
MWT	8·4 (1·8)	7·6 (3·0)	0·88	7·4 (2·3)	9·7 (2·8)	1·32	8·8 (2·5)	15·1 (2·7)	1·72	1·47 (1·01 to 2·14); p=0·044	0·77 (0·52 to 1·13); p=0·173
SART-NO GO	8·0 (1·8)	8·1 (1·8)	1·0	9·2 (2·0)	7·5 (1·9)	0·82	8·5 (2·0)	7·1 (1·9)	0·84	0·81 (0·67 to 0·99); p=0·038	0·97 (0·81 to 1·17); p=0·765
SART-GO	3·5 (0·7)	2·7 (0·7)	0·76	3·5 (1·1)	2·1 (0·6)	0·6	3·2 (0·7)	2·5 (0·6)	0·79	0·79 (0·56 to 1·12); p=0·176	0·77 (0·54 to 1·20); p=0·141
SART-total	11·5 (2·1)	11·4 (2·1)	1·0	12·5 (2·1)	10·0 (2·2)	0·8	11·6 (2·1)	10·4 (2·2)	0·89	0·80 (0·64 to 1·00); p=0·053	0·90 (0·71 to 1·14); p=0·370
CGI-C EDS improved (n/N [%])	..	..	14/25 (56%)	..	..	19/26 (73%))	..	..	24/28 (86%)	..	..
CGI-C cataplexy improved (n/N [%])	..	..	6/25 (24%)	..	..	9/26 (35%)	..	..	8/28 (29%)	..	..
EQ-5D	64 (19·2)	70·2 (17·7)	..	65·3 (21·3)	73·8 (17·8)	..	58·7 (19·4)	72·6 (16·5)	..	..	..
Patient global opinion improved (n/N [%])	..	..	14/25 (56%)	..	..	24/28 (81%)	..	..	24/28 (86%)	..	..
ESS responder (post-hoc analysis; n/N [%])	..	..	4/30 (13%)	..	..	14/31 (45%)	..	..	15/33 (46%)	4·4 (2·1 to 9·2); p<0·0006	1·0 (0·68 to 1·6); p=0·908
Cataplexy rate (post-hoc analysis)	0·43 (0·7)	0·39 (0·6)	0·92	0·52 (0·6)	0·18 (0·4)	0·38	0·4 (0·6)	0·26 (0·5)	0·64	0·38 (0·16 to 0·93); p=0·034	0·54 (0·24 to 1·23); p=0·138

Data are mean (geometric SD) unless otherwise stated. CGI-C=clinical global impression of change. CGI-S=clinical global impression of severity. EQ-5D=European quality of life questionnaire. ESS=Epworth Sleepiness Scale. SART=Sustained Attention Reaction Test. MWT=Maintenance of Wakefulness Test. *=change calculated as final÷baseline, unless otherwise stated.

Table 2: **Efficacy results (intention-to-treat population)**

group, but we recorded no statistically significant difference between pitolisant and modafinil (table 2).

NO GO error scores in the SART were similar between baseline and end of treatment in the placebo group, whereas they decreased in the pitolisant group, with a statistically significant difference between groups (table 2). Changes in the modafinil and pitolisant groups, however, were not statistically different. We recorded no differences in changes from baseline between either pitolisant and placebo or pitolisant and modafinil in either the SART GO scores or total SART scores (table 2).

The proportion of patients who had improvements in EDS assessed with the CGI-C by the end of treatment was largest in the modafinil group and smallest in the placebo group (table 2). We saw little between-group difference in change in severity of cataplexy assessed with CGI-C. EQ-5D values were much the same in the three groups whereas patient global impression on treatment improved only slightly more for pitolisant or modafinil than for placebo. The small number of occurrences of other parameters collected in the sleep diaries (hallucinations, sleep attacks, and severe sleepiness) precluded any formal comparison between groups.

In post-hoc analyses, pitolisant was superior to placebo but not non-inferior to modafinil in terms of improvement in cataplexy rate from baseline (table 2, appendix). In other post-hoc analyses, the percentage of responders (with final ESS scores of 10 or lower) also differed between the pitolisant and placebo groups and were similar between pitolisant and modafinil (table 2).

Adverse events occurred in 22 patients receiving pitolisant, 26 receiving modafinil, and 10 receiving placebo (table 3). The most frequent adverse events were headache for the three groups, insomnia, abdominal discomfort, and nausea for pitolisant, and abdominal discomfort, nausea, diarrhoea, dizziness, anxiety, and irritability for modafinil. We recorded no clinically relevant between-group differences in terms of intensity or resolution across the three groups. Two serious adverse events occurred in each group, all of which were deemed unlikely to be related to treatment. Nine adverse events reported as severe occurred during the treatment period, of which six were regarded as treatment-related: one with pitolisant (abdominal discomfort) and five with modafinil (abdominal pain, abnormal behaviour, amphetamine-like withdrawal symptoms, lymphoadenopathy, and inner ear disorders; table 3).

With regards to drug abuse potential, no patient on placebo or pitolisant had DSM-5-defined[19] withdrawal syndrome during the withdrawal phase, compared with three patients in the modafinil group. Blood chemistry tests or haematological or cardiovascular parameters did not change in the three study group (data not shown).

Discussion

In our study, treatment with pitolisant—to the best of our knowledge the first H3-receptor inverse agonist to be introduced in human therapy (panel)[23,24]— reduced EDS compared with placebo, but was not non-inferior to treatment with modafinil. Compared with placebo, EDS was improved with pitolisant in both subjective and objective assessments. Mean ESS decreased progressively from baseline to final to a maximum of 5·8 units with pitolisant, the difference with placebo being about 3 units, which are two clinically-relevant findings (table 2, figure 3). Laboratory measures of EDS and vigilance were also improved: time awake in a dark environment, as measured by the MWT, was better with pitolisant by a factor of 1·47 versus placebo; patients' attention level as measured by SART (NO GO

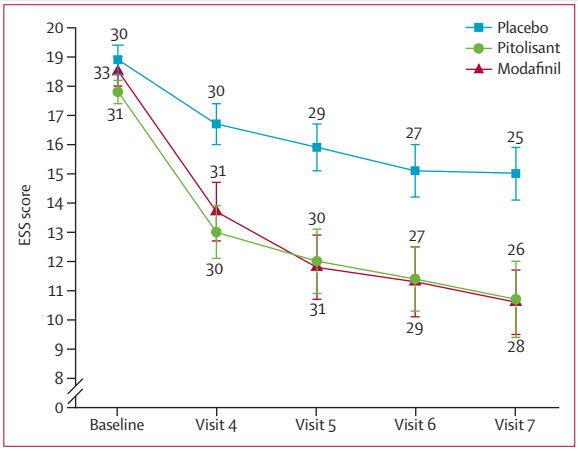

Figure 3: **Changes in Epworth sleepiness scale (ESS) score**
Data points are mean and error bars are SEM.

See **Online** for appendix

	Placebo (N=30)	Pitolisant (N=31)	Modafinil (N=33)
Adverse events			
Headache	6 (20%)	11 (35%)	6 (18%)
Insomnia	0	3 (10%)	0
Abdominal discomfort or pain	0	2 (6%)	6 (18%)
Nausea	2 (7%)	2 (6%)	1 (3%)
Diarrhoea	0	1 (3%)	4 (12%)
Dizziness	0	1 (3%)	4 (12%)
Anxiety	0	0	2 (6%)
Irritability	0	1 (3%)	2 (6%)
Weight increased	2 (7%)	1 (3%)	0
Amphetamine-like withdrawal symptoms	0	0	3 (10%)
Serious adverse events			
Abdominalk pain or discomfort	0	1 (3%)	1 (3%)
Abnormal behaviour	0	0	1 (3%)
Amphetamine-like withdrawal symptoms	0	0	1 (3%)
Inner ear disorders	0	0	1 (3%)
Lymphoadenopathy	0	0	1 (3%)

Data are number of patients (%).

Table 3: **Adverse events**

Panel: Research in context

Systematic review

We searched PubMed and Web of Knowledge for articles using the following search terms: "histamine H3 receptor inverse agonist clinical trial in narcolepsy", and "histamine H3 receptor antagonist clinical trial in narcolepsy". We did our last search on July 15, 2013. We applied no language restrictions. We retrieved two articles. The first article[14] reported data for the effects of pitolisant on a mouse model of narcolepsy and in a small population of patients with narcolepsy treated for 1 week during a single-blind trial. The second article[24] was a short review of the discovery of the H3 receptor and preclinical data for pitolisant, and a summary of clinical data.

Interpretation

Results from the single-blind trial[14] suggested that pitolisant might be beneficial for patients with narcolepsy but these findings required confirmation in a longer, double-blind trial. To our knowledge, the present trial is the first double-blind trial of a histamine H3 receptor antagonist in narcolepsy with or without cataplexy. Our findings suggest that excessive daytime sleepiness can be improved by pitolisant for at least 2 months, as judged by two objective tests in addition to the ESS, and that the drug might also have some anticataplectic activity. Whereas its wake-promoting activity does not differ from that of modafinil, a reference drug in this pathology, it seems to be better tolerated.

index) was also improved compared with placebo (table 2). CGI improvement was high with both pitolisant and placebo, possibly because of the frequent visits to the investigators, which might have enhanced any placebo effect.

The effects of pitolisant and modafinil on all EDS measures did not differ substantially, although the non-inferiority test was not statistically significant, possibly due to the small number of patients assessed.

61% of patients had cataplexy during the trial, although 35% continued their usual anticataplectic drugs. In a post-hoc analysis of patients with cataplexy attacks during the trial, the number of daily attacks improved in the pitolisant group compared with placebo but not compared with modafinil.

All three treatments were well tolerated, with mostly minor adverse events; headache tended to be more frequent with pitolisant and gastrointestinal disorders were more frequent with modafinil. Typical withdrawal syndrome[19] was detected in three patients at abrupt interruption of modafinil (with one patient having drug withdrawal symptoms for 5 days) but not with pitolisant. This finding is consistent with preclinical drug abuse signals with modafinil but not pitolisant,[25] and the observations of accumbal dopamine release after modafinil in animals and human volunteers.[26,27] Enhancement by pitolisant of the activity of histaminergic and other major alerting systems (cortical noradrenergic, dopaminergic, and cholinergic neurons), including in hypocretin-deficient mice, accounts for its wake-promoting action.[14,28] Pitolisant, however, does not activate accumbal dopaminergic neurons, accounting for the complete absence of psychomotor activation and behavioural sensitisation, and the low addiction liability,[24,28] thereby indicating that it does not act as a typical psychostimulant.

Our study had some limitations. Its short duration did not allow prediction of whether tolerance can develop on continuation; also, the flexible dosage and multiple visits could have affected the efficacy, with less responsive patients being more likely to be titrated to the highest dose. The exclusion of children, severely ill patients, those with unstable comorbidities, and those who refused to potentially receive a placebo during the trial does not allow extrapolation of our efficacy and safety findings to these populations. Furthermore, patients who had previously received modafinil could have been aware that they were receiving it because of its effects, thus negating our masking strategy, affecting some patients' response to treatment. Our assessment of withdrawal syndrome might also be subject to questioning because early withdrawal effects might have been missed if they were not recalled or reported by patients at the later assessment and if the scale used was not sensitive enough. The CGI-C we used is a non-validated measure in narcolepsy. And finally, continuation of anticataplectic treatments in a subpopulation of patients precludes extrapolation of our findings to drug-free patients. A trial assessing the anticataplectic activity of pitolisant in drug-free patients (NCT 01800045) and a long-term trial in general patients (NCT 01395606) are ongoing.

Our findings suggest that pitolisant is well tolerated compared with modafinil and decreases EDS of narcolepsy in a large proportion of patients compared with placebo. If these findings are supported by further studies, it could offer a promising treatment in narcolepsy.

Contributors

J-CS participated in the conception and design of the study, and wrote the first draft of the paper. YD and GM contributed to the conception and design of the study, data acquisition and interpretation, and revisions to the paper. CB participated in the study design and co-ordination, and data acquisition and interpretation. GJL participated in data acquisition and interpretation and revised the paper. IA participated in data acquisition. AR participated in data acquisition and revised the paper. PL developed the statistical analysis plan and revised the paper. C-LD participated in the conception, design, and organisation of the study. J-ML participated in the conception, design, and organisation of the study.

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Conflicts of interest

YD has received funds for speaking and board engagements with UCB, Cephalon, Jazz, Novartis, and Bioprojet. CB has received honoraria for advisory boards or lectures from Boehringer Ingelheim, Cephalon, GSK, Jazz, Lundbeck, Pfizer, ResMed, Respironics, UCB Pharma, and Vifor Pharma; his research has been supported by the Swiss National Science Foundation, the Swiss Heart Association, ResMed, Respironics, UCB, Pharma, and Vifor Pharma. IA has received funds for speaking and board engagements with UCB and Jazz. GJL has received funds for speaking for UCB and MSD, and board engagements with UCB. AR has received funds for speaking for Cephalon and Lundbeck, and board engagement with Cephalon. PL has received funds for speaking with Bayer, Abbott, Merck, and Novartis. GM has received speaker honoraria from Lundbeck Pharma, UCB Pharma, and Cephalon; he is participating in advisory boards for UCB Pharma and Genzyme; and he has received financial support for investigator-initiated studies from Cephalon Germany and UCB Pharma. C-LD was an employee of Bioprojet. J-ML and J-CS are employees and shareholders of Bioprojet.

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