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

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- To evaluate the efficacy of pitolisant (5, 10, 20,40mg/d in the Double Blind Period and 5, 10, 15, 20, 30, 40mg/d in the Open Label Period) in reducing residual Excessive Daytime Sleepiness (EDS) and the number of cataplectic episodes (for...

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Sleep disturbances (incl subtypes)
Study type	Interventional

Summary

ID

NL-OMON53057

Source
ToetsingOnline

Brief title
P11-06/Pitolisant

Condition

- Sleep disturbances (incl subtypes)

Synonym
Hypersomnia, Sleep disorder

Research involving
Human

Sponsors and support

Primary sponsor: Bioprojet
Source(s) of monetary or material Support: Bioprojet

Intervention

Keyword: Cataplexy, Children (age between 6 and 17), Narcolepsy, Pitolisant

Outcome measures

Primary outcome

Change in the intensity and frequency of symptoms of narcolepsy (EDS and cataplexy) as measured by the Ullanlinna Narcolepsy Scale (UNS) between baseline: [V1 score (D-14) + V2 score (D0)]/2 and the end of treatment: [V6 score (D49) + V7 score (D56)]/2. We will compare the results between pitolisant and placebo groups.

Secondary outcome

- Changes in EDS as measured by the maintenance of wakefulness test (MWT) between baseline and V7, in pitolisant and placebo groups.

- Change in EDS measured by the Paediatric Daytime Sleepiness Scale (PDSS) between baseline: [V1 score (D-14) + V2 score (D0)]/2 and the end of treatment: [V6 score (D49) + V7 score (D56)]/2. We will compare the results between pitolisant and placebo groups.

- Changes in EDS as measured by the Child and Adolescent Sleepiness Scale (CASS) between baseline and the end of treatment, in pitolisant and placebo

groups.

- Changes in the average number of cataplexy episodes per weeks (recorded in sleep diary by patient and/or parent/teacher) between the 2 weeks of baseline and the 2 weeks of end study treatment period (V6, V7), in pitolisant and placebo groups.

- 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 (V4 to V7), in pitolisant and placebo groups.

- Severity of EDS measured by the Clinical Global Impression of severity and change. Changes between baseline and V6, V7, in pitolisant and placebo groups.

- Severity of cataplexy measured by the Clinical Global Impression of severity and change. Changes between baseline and V6, V7, in pitolisant and placebo groups.

- Changes between baseline and V6, V7 will be compared for the Ullanlina narcolepsy test, in pitolisant and placebo groups.

- Changes between baseline and V6 will be compared for the TEA-Ch test, in pitolisant and placebo groups.

- Comparison between placebo and pitolisant groups on:

Withdrawal symptoms questionnaire (DSM IV)

Patients* Global Opinion on treatment effect at the end of treatment if able to express himself. If not will be reported either by parents or teachers.

- Changes between baseline and at each visit of the open-label period in EDS.

- Safety assessment will be done on monitoring of adverse events, physical examination, vital signs, ECG and Blood Laboratory tests modifications and the

mood appraisal throughout the study.

Study description

Background summary

Pitolisant (BF2.649) is an orally active histamine H3 receptor antagonist / inverse agonist. After having determined its pharmacological profile showing that pitolisant enhances the histaminergic transmissions in brain and thereby improves vigilance, learning and memory and displays pro-cognitive properties, this product was subject to a number of clinical trials gathering more than 300 adults suffering from narcolepsy with or without cataplexy, and treated by pitolisant, placebo, or comparator. The results obtained on EDS and on cataplexy are in favour of BF2.649 (in a statistically significant way with regard to placebo). Besides, by taking into account all patients who were administered pitolisant (i.e. 1000 patients in various indications), the safety profile was proven to be quite satisfactory, thus allowing to envisage the use of this drug in the paediatric population.

Study objective

- To evaluate the efficacy of pitolisant (5, 10, 20,40mg/d in the Double Blind Period and 5, 10, 15, 20, 30, 40mg/d in the Open Label Period) in reducing residual Excessive Daytime Sleepiness (EDS) and the number of cataplectic episodes (for patients with cataplexy)
- To determine safety in children and adolescents
- To assess the long-term safety of BF2.649 in the treatment of EDS in narcoleptic patients with or without cataplexy.
- To assess the drug-drug interactions with possible concomitant therapies.
- To assess the efficacy of long-term therapy with BF2.649 on EDS after a prolonged treatment period.

Study design

Double blind, multicentre, randomized, placebo-controlled trial followed by a prolonged open-label period

Double blind phase of the study:

V0 - Screening visit and start of wash out period (Day-28 = only for patients under prohibited medications and cataplectic patients under anti-cataplectic treatment).
V1 - Screening visit and Baseline period (Day -14)
V2 - Randomization and start of escalating period (Day 0)

V3 - Dose adjustment visit (D 14 ± 2 days)
V4 - Dose adjustment visit (D21 ± 2 days)
V5 - Dose adjustment visit (D28 ± 2 days)
V6 - Control treatment visit (D49 ± 2 days)
V7 - End of Double Blind Period (D56 ± 2 days)
T1 - Telephone contact at D59 (± 1 day)
V8 - End of study visit after 1 week of placebo wash out or (D63 ± 2 days) / Start of Open label or Premature withdrawal visit (within 5 days after last treatment intake)

Open-label phase of the study:
Patients completing V8 will have the possibility to continue the treatment with pitolisant in open conditions until BF2.649 (pitolisant) is available on the market for children/adolescent from 6 to 17 years.

V9 - Dose adjustment visit (D77 ± 2 days)
V10 - Dose adjustment visit (D84 ± 2 days)
T2 - Telephone contact at D91 (± 1 day)
V11 - Dose adjustment visit (D112 ± 7 days)
V12 - Dose adjustment visit (D196 ± 7 days)
V13 - Dose adjustment visit (D364 ± 7 days)
All subsequent visits are performed each 6 months.

Inclusion period 4 weeks (including 2-week baseline period). Followed by, Double-blind period, treated by pitolisant or placebo for 8 weeks,
Followed by, Single blind wash-out period, treated by placebo for 1 week and then Followed by a prolonged open-label period depending on patient wish.

Intervention

The total treatment duration of this double blind study is 8 weeks. Patients will start pitolisant (or placebo) treatment with escalating doses scheme on the first 4 weeks, as follows:
- V2 - 5 mg of BF2.649 or placebo / day during the first week,
10 mg of BF2.649 or placebo /day during the second week,
- V3 - Increase to 20 mg/d or maintain at 10 mg/d or reduce to 5 mg/d of BF2.649 (or placebo) per day for 7 days depending on efficacy and tolerability.
- V4 - It will also be possible to reduce the dose administered to the patients, or to increase it without exceeding 40 mg/d. Patients with a weight less than 40kg could be treated with a maximum daily dose of 20mg.
- V5 - It will be possible to reduce the dose administered to the patients, but not to increase it. As from V5 onwards, no dosage change of the study treatment will be authorized.
- At the end of the double blind treatment (V7), the investigator will provide placebo to all patients for the one-week wash out period.

In open-label period patients will start pitolisant treatment with escalating

doses scheme, as
follows:
- V8 - 5 mg of BF2.649 or placebo / day during the first week.
10 mg of BF2.649 or placebo /day during the second week.
- V9 - The third week according to investigator prescription and evaluation on efficacy and tolerance, the dose will be maintained or increased at 20mg/d or reduced at 5 mg/d.
- V10 - According to investigator prescription and evaluation on efficacy, tolerance and weight, the dose will be maintained, reduced or increased at 5, 10, 15, 20, 30 or 40mg/d (only if patient weight is above 40kg) for the next 4-week.

During the phone contact (T2), in opinion of investigator, the dose could be re-adjusted according to the effectiveness/tolerability of treatment to patient. In case of need, it is possible to plan a visit on site within the week following the telephone contact for obtaining new bottles of treatment with the corresponding dose. The other dose decrease, from 40 to 20 and 10 to 5 mg, in agreement with the investigator don't need to visit. The bottles contain a suitable number of tablets to decrease the dose.

- V11 - According to investigator prescription and evaluation on efficacy, tolerance and weight, the dose will be maintained, reduced or increased at 5, 10, 15, 20, 30 or 40mg/d (only if patient weight is above 40kg) for the next 3-month.
- V12 - According to investigator prescription and evaluation on efficacy, tolerance and weight, the dose will be maintained, reduced or increased at 5, 10, 15, 20, 30 or 40mg/d (only if patient weight is above 40kg) for the next 6-month.
- All subsequent visits, the treatment dispensation will be done like V12.

Study burden and risks

As pitolisant is a new treatment, not all of its adverse effects are known, although the most commonly observed adverse effects with pitolisant in comparison with placebo in the previous 25 studies were: insomnia, headache, nausea, gastric disorders, anxiety, hallucinations, irritability, dizziness, depression, vomiting, vertigo.
Most of these reported adverse effects were mild or moderate. All these effects were transient and went away on their own or when the treatment was stopped. In all 25 clinical trials, no serious side effects durably associated with pitolisant were observed. There were no serious sequelae following treatment-related adverse events.
In addition, all treatments carry a risk of an allergic reaction.
Blood sampling is usually well tolerated. Blood is drawn into a small syringe through a needle inserted into a vein. A mild local reaction at the needle insertion site may occur. On request, a local anesthetic can be used for the needle insertion. The amount of the blood sample (5 mL per sample for the

laboratory tests, or a total of 10 mL for the first part of the study) will have no repercussions on the child*s health.

Possible benefits:
Both phase II and III studies performed in narcoleptic patients with or without cataplexy, all of them being treated by pitolisant or placebo during 8 weeks and analysed, confirmed the efficacy of pitolisant on excessive daytime sleepiness with effects statistically superior to those of the placebo.
In addition, the analysis of sleep diaries completed by the patients during 7 days prior to each visit showed a possible reduction of the risks of cataplexy.

Contacts

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Scientific
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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adolescents (12-15 years)
Adolescents (16-17 years)
Children (2-11 years)

Inclusion criteria

1) Male and female children from 6 to less than 18 years of age (until V8) suffering from narcolepsy with or without cataplexy - meeting the International Classification of Sleep Disorders (ICSD-3) criteria (narcolepsy type 1 and 2). Diagnosis confirmed with polysomnography and Multiple Sleep Latency Test for patients without cataplexy (if these examinations were not performed within the last 12 months), 2) PDSS score >= 15 during baseline period (V1+V2) / 2., 3) Patients should be free of non-authorized medication, in particular psychostimulant treatments as from the screening visit (V0) onwards., 4) Parents - and patients old enough to understand who have expressed a willingness to participate in the study, who have signed and dated the informed consent form prior to beginning protocol required procedures., 5) In the opinion of the investigator, the patient must have adequate support to comply with the entire study requirements as described in the protocol (e.g., transportation to and from trial site, self rating scales and diaries completion, drug compliance, scheduled visits, tests). , 6) Female pubescent patients shall use a birth control method, judged efficient by the investigator, throughout the study and during the month following treatment discontinuation., 7) Patients should benefit from appropriate healthy insurance system (only applicable where mandatory e.g. in France).

Exclusion criteria

1) Any other conditions that can be considered the primary causes of EDS: such as sleep related breathing disorders as defined by a sleep Apnea Index >= 5 per hour or/and an Apnea/Hypopnea Index >= 10 per hour, chronic sleep deprivation, circadian sleep wake rhythm disorder or any other medical or neurological causes that could account for narcolepsy symptoms associated with EDS., 2) Cataplectic patients treated by anticataplectics (SNRI, SSRI, sodium oxybate) which are not under a stable treatment since at least 4 weeks at the time of inclusion (V2). , 3) Patients treated for cataplexy or any other pathology, by tricyclic antidepressants (clomipramine, imipramine, mirtazapine, desmethylimipramine and protriptyline) are not authorized because they display histamine H1 receptor antagonist activity., 4) The use of pitolisant within a 30-day period prior to initial screening visit (V0) for this trial., 5) Current or recent (within one year) history of a substance abuse or dependence disorder including alcohol abuse as defined in Diagnostic and Statistical Manual of Mental Disorders (DSM-IV)., 6) Any significant abnormality of the electrocardiogram and particularly Fridericia*s QTc interval (QTcF = QT/3* 60/HR) higher than 450ms. , 7) Patients with severe depression (CDI >= 16), 8) Patient with suicidal risk (C-SSRS) , 9) Positive urinary drug testing (test applicable to patients from 12 years), 10) Pregnancy (defined as positive β-HCG blood test), breast-feeding, or patients and unable to use an efficient method

of birth control shall not be included in the study (for pubescent female only)., 11) Patients with severe hepatic Impairment (Child Pugh C) or with any other significant abnormality in the physical examination or clinical laboratory results., 12) Psychiatric and neurological disorders, such as moderate or severe psychosis or dementia, depression, history of seizure disorder or other problem that, in the investigator*s opinion, would preclude the patient*s participation and completion of this trial or comprise reliable representation of subjective symptoms., 13) Active clinically significant illness, including unstable cardiovascular, endocrine, neoplastic, gastrointestinal, haematological, hepatic, immunologic, metabolic, neurological (other than narcolepsy/cataplexy), pulmonary, and/or renal disease which could interfere with the study conduct or counter-indicate the study treatments or place the patient at risk during the trial or compromise the study objectives., 14) Prior severe adverse reactions to CNS stimulants., 15) Known hypersensitivity to the tested treatment including active substance and excipients., 16) The inability to continue daily activities safely, without the use of treatment against EDS., 17) Any patient presenting congenital galactosemia, glucose-galactose malabsorption or lactase deficiency due to the presence of lactose in investigational treatments., 18) Patients participating in another study or being in a follow-up period for another study., 19) Cannot be contacted in case of emergency.

Study design

Design

Study phase:	3
Study type:	Interventional
Intervention model:	Other
Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)
Control:	Placebo
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	07-09-2017
Enrollment:	10

Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	pitolisant
Generic name:	histamine H3-receptor inverse agonist
Registration:	Yes - NL outside intended use

Ethics review

Approved WMO Date:	05-09-2016
Application type:	First submission
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl

Approved WMO Date:	23-09-2016
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl

Approved WMO Date:	26-04-2017
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl

Approved WMO Date:	07-06-2017
Application type:	First submission
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl

Approved WMO

Date:	04-03-2019
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden)
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Approved WMO

Date:	18-10-2019
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden)
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Approved WMO

Date:	04-11-2020
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden)
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Approved WMO

Date:	16-01-2021
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden)
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Approved WMO

Date:	18-02-2022
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden)
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Approved WMO

Date:	11-03-2022
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden)
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Approved WMO

Date:	19-05-2022
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
EudraCT	EUCTR2013-001506-29-NL
CCMO	NL58537.058.16