A DOUBLE-BLIND, PLACEBO-CONTROLLED, PARALLEL-GROUP, MULTICENTER STUDY OF THE EFFICACY AND SAFETY OF PREGABALIN AS ADJUNCTIVE THERAPY IN CHILDREN 4 -16 YEARS OF AGE WITH PARTIAL ONSET SEIZURES

Published: 24-06-2011
Last updated: 29-04-2024

The primary objective of this study is to evaluate the efficacy of 2 dose levels of pregabalin (Level 1: 2.5 mg/kg/day; maximum 150 mg day and Level 2: 10 mg/kg/day; maximum 600 mg day) compared to placebo as an adjunctive treatment in reducing the...

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

Summary

ID

NL-OMON39878

Source
ToetsingOnline

Brief title
A0081041 - Pregabalin study for children age 4-16

Condition

- Seizures (incl subtypes)

Synonym
Epilepsy with partial onset seizures

Research involving
Human

Sponsors and support

Primary sponsor: Pfizer
Source(s) of monetary or material Support: Pharmaceutical Industry

Intervention

Keyword: Adjunctive Therapy, Double blind, Epilepsy, Pregabalin

Outcome measures

Primary outcome

The primary endpoint will be the log-transformed (loge) 28-day seizure rate for all partial onset seizures collected during the 12 week double-blind treatment phase. Data from the 1-week double-blind taper phase will not be used in the efficacy analyses. Results will be reported as *percent reduction in seizures* relative to placebo. The 28-day seizure rate will be calculated as follows for the double-blind period:

# of seizures in the double-blind phase

of study

28 day seizure rate =

X 28

# of days in period - # of missing diary

days in period

When the log-transformation is used, the quantity 1 is added to the 28-day

seizure rate for all subjects to account for any possible "0" seizure incidence. This will result in the following primary efficacy measure: loge (28-day seizure rate +1). For example, a difference between one of the pregabalin doses and placebo of -0.400 on the log transformed scale for the 28-day seizure rate, translates into a 33% reduction in the 28-days seizure rate of the pregabalin group from the placebo group (ie, 100%*[exp-0.400-1]=-33%]).

The 28-day seizure rate for the baseline phase will be calculated similarly.

Secondary outcome

Responder Rate, defined as subjects who have a * 50% reduction in partial seizure rate from baseline during the double-blind treatment phase. Subjects meeting this criterion will be considered a favorable outcome.

Study description

Background summary

Epilepsy is a common disorder in childhood affecting 4 to 5 of every 1000 children. Although epilepsy is often well controlled with existing antiepileptic drug (AED) therapy, more than 25% of pediatric patients have seizures that are uncontrolled by currently available agents, or have adverse effects related to AEDs that complicate their seizure control. In addition, children with epilepsy often suffer from impaired academic performance and have a higher likelihood of developing behavioral difficulties, which may persist into adulthood. Early age of onset and a higher number of total lifetime seizures are the strongest correlates of academic underachievement. Therefore, the availability of a new AED that has been shown to improve seizure control and that is generally well tolerated is needed.
Pregabalin is approved in more than 50 countries, including the United States (US) and the European Union (EU). In the US and EU, pregabalin is indicated for the adjunctive

treatment of adult patients with partial onset seizures. In addition, pregabalin is indicated for the treatment of central and peripheral neuropathic pain (EU), and for the management of neuropathic pain associated with postherpetic neuralgia and diabetic peripheral neuropathy and for fibromyalgia (US). In the EU, pregabalin is also approved for the treatment of Generalized Anxiety Disorder in adults. The approved dose range for the adjunctive treatment of partial onset seizures in adults is 150 to 600 mg/day, administered twice daily (BID) or three times daily (TID). The most common adverse effects reported with pregabalin in placebo-controlled adjunctive trials of pregabalin in adults with partial onset seizures were dizziness (32%) and somnolence (22%). Since initial market approval of Lyrica in 2004 through Jan 31, 2011, it is estimated that more than 11,700,000 patient-years of exposure will have accumulated worldwide. More detailed information, including efficacy results in adults and the possible risks associated with administration of pregabalin, are summarized in the Investigator*s Brochure which serves as the Single Reference Safety Document for this study.

This study is one of several studies that will be conducted to assess the safety and efficacy of pregabalin in pediatric subjects with epilepsy and address post approval commitments to US and EU regulatory authorities.

Study objective

The primary objective of this study is to evaluate the efficacy of 2 dose levels of pregabalin (Level 1: 2.5 mg/kg/day; maximum 150 mg day and Level 2: 10 mg/kg/day; maximum 600 mg day) compared to placebo as an adjunctive treatment in reducing the frequency of partial onset seizures in pediatric subjects 4 to 16 years of age.

Study design

Study A0081041 is a double-blind, placebo-controlled, randomized, parallel-group, multicenter study to evaluate dose Level 1 (2.5 mg/kg/day; maximum 150 mg/day) and dose Level 2 (10 mg/kg/day; maximum 600 mg/day) of pregabalin administered BID (ie, the dose is equally divided into two daily administrations) as adjunctive therapy in pediatric subjects 4-16 years of age with partial onset seizures.

The study is composed of 3 phases:
* 8 week baseline phase.
* Double blind assessment phase 12 weeks of double-blind treatment which includes 2 weeks dose escalation followed of fixed-dose treatment.
* 1 week double-blind taper phase.

Intervention

Subjects will be randomized in a double-blind manner to a fixed dose of either of the following:
* Placebo
* Level 1: Pregabalin 2.5 mg/kg/day (maximum 150 mg/day)
* Level 2: Pregabalin 10 mg/kg/day (maximum 600 mg/day)
Note that dosing will be adjusted for subjects <30 kg in body weight. For lower weight subjects (<30 kg) subjects randomized to Level 1 or Level 2 of pregabalin, the dose will be adjusted in order to achieve equivalent exposure across the weight range of pediatric subjects to be enrolled in the study. Pregabalin clearance is increased in children <30 kg which results in lower exposure for the same mg/kg/day dose compared with children * 30 kg.

Study burden and risks

The most common side effects reported out of 17,727 subjects who took pregabalin in past studies are:
* dizziness
* sleepiness

Contacts

Public
Pfizer

East 42nd Street 235
New York NY 10017
US
Scientific
Pfizer

East 42nd Street 235
New York NY 10017
US

Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

Subject eligibility should be reviewed and documented by an appropriately qualified member of the investigator*s study team before subjects are included in the study. Subjects must meet all of the following inclusion criteria to be eligible for enrollment into the study:
1. Evidence of a personally signed and dated informed consent document indicating that
the subject and/or parent/legally acceptable representative has been informed of all
pertinent aspects of the study. When there are two parents or two legally acceptable
representatives, consent should be obtained from both of the child*s parents/legal
representatives if present at the meeting where the informed consent document is signed. Subject to local regulations whenever the minor is able to give assent, the minor*s assent must also be obtained.
2. Subjects and/or parent(s)/legally acceptable representative who are willing and able to
comply with scheduled visits, treatment plan, laboratory tests, and other study procedures.
3. Subjects and/or parent(s)/legally acceptable representative must be considered willing
and able to complete daily seizure diaries and monitor seizure frequency.
4. Male and female epilepsy subjects, 4 to 16 years of age inclusive on the date of the
Screening Visit.
5. Diagnosis of epilepsy with partial onset seizures classified as simple partial, complex
partial or partial becoming secondarily generalized, according to the International
League Against Epilepsy (ILAE)3 Diagnosis must be established by:
- Subject*s history (eg, description of seizures excluding confounding disorders such as pseudoseizures, syncopes etc) family history and neurological exam.
- Subjects must have had a contrast enhanced computed tomography (CT) or magnetic resonance imaging (MRI) scan of the brain and EEG testing within 24 months of the Screening Visit. Results must be consistent with the
diagnosis of focal-onset epilepsy and must demonstrate that no abnormality is
likely to be progressive.
- Confirmation of diagnosis by independent reviewer before randomization.
6. Must have a partial onset seizure frequency of at least 3 seizures per 28-day period
prior to screening. Must have a partial onset seizure frequency of *6 seizures and no
continuous 4 week seizure free period during the 8 week baseline phase prior to
randomization.
7. Currently receiving a stable dose of 1 to 3 antiepileptic drugs (stable within 28 days

prior to screening). Benzodiazepine medication used on a regular basis at a stable
dosage will be considered 1 of the concurrent antiepileptic treatments. A previously
implanted Vagus nerve stimulator (VNS) for the treatment of epilepsy is allowed and
will be considered one of the 3 antiepileptic treatments.
8. A 12-lead ECG at screening without significant abnormal findings as determined by
the investigator and confirmed by the Central ECG Reader.

Exclusion criteria

1. Primary generalized seizures (including in the setting of co-existing partial onset
seizures) which include for example:
- Clonic, tonic and clonic-tonic seizures (note that partial onset seizures that become secondarily generalized are not exclusionary).
- Absence seizures.
- Infantile spasms.
- Myoclonic, myoclonic atonic, myoclonic tonic seizures.
2. Lennox-Gastaut syndrome, Benign Epilepsy with Centrotemporal Spikes (BECTS) and Dravet syndrome. 3. A current diagnosis of febrile seizures, or seizures related to an ongoing acute
medical illness. Any febrile seizures within 1 year of screening. 4. Status epilepticus within 1 year prior to screening. 5. Seizures related to drugs, alcohol, or acute medical illness. 6. Any change in AED regimen (type of medication or dose) within 28 days of the Screening Visit or during the Baseline Phase. 7. Progressive structural CNS lesion or a progressive encephalopathy.
8. Progressive errors of metabolism. 9. Known or suspected chronic hematologic, hepatic or renal disease (AST and ALT above 3 times the upper limit of normal (ULN); or bilirubin, BUN, or creatinine above 2 times the ULN within the previous 6 months prior to screening). 10. Estimated creatinine clearance (ClCR) <80 mL/min/1.73 m2. 11. Other severe acute or chronic medical or psychiatric condition (eg, current major depressive disorder;schizophrenia or other psychoses) or laboratory abnormality that may increase the risk associated with study participation or study medication administration or may interfere with the interpretation of the study results and, in the judgment of the investigator, would make the subject inappropriate for entry into this study. 12. Pregnant or nursing females (females who are menarchal must have a negative pregnancy test); menarchal females of childbearing potential who are unwilling or unable to use an acceptable method of contraception from at least 14 days prior to the first dose of study medication until completion of the study.
13. Taking any non-antiepileptic (non-AED) medication that could alter the effectiveness
of the subject*s medication, response, seizure frequency or characteristics. Medications for Attention Deficit/Hyperactivity Disorder will be permitted if medication doses are stable and remain so throughout the duration of study. A
ketogenic diet will also be allowed given that the diet is adhered to for the duration of
the study. 14. The concomitant use of gabapentin is prohibited. 15. Use of cocaine, phencyclidine (PCP), or other illegal or illicit drugs is prohibited. Use of amphetamines, barbiturates, opiates, or benzodiazepines without a valid current prescription is

prohibited.
16. History of lack of efficacy for treatment of epilepsy with pregabalin at presumed efficacious doses. 17. Known allergy or intolerance to pregabalin or other *2* ligands (eg, gabapentin).
18. Prior participation in a pregabalin clinical trial.
19. Treatment with pregabalin for any reason within 60 days prior to screening. 20. History of sensitivity to heparin or heparin induced thrombocytopenia. 21. Unwilling or unable to comply with the Life Style Guidelines. 22. Not reasonably expected to complete the trial.
23. Participation in other clinical studies within 30 days before the current study begins
 and/or during study participation. 24. Subjects whose parents/legally acceptable representatives are investigational site staff
members or subjects whose parents/legally acceptable representative are Pfizer
 employees directly involved in the conduct of the trial. 25. Any subjects considered at risk of suicide based on the MINI-KID and C-SSRS
Lifetime (subjects age *6 years) or CBCL (subjects <6 years) or likely to self harm
 based on clinical judgment. Based on the judgment of the investigator, a subject
 should be excluded or a risk assessment should be done by a qualified mental health
 professional based on responses to suicidality assessments and if the subject has had
 suicidal ideation in the last 6 months prior to screening, suicidal behaviors or attempts
 within the past year or current major psychiatric disorders that are not explicitly permitted in the inclusion/exclusion criteria. A risk assessment should also be performed in any child <6 years of age who has ever exhibited any potentially
self-injurious or high-risk behaviors such as hurting himself or herself, or unusual
 behaviors such as running into traffic or using items as weapons (eg, knife, bat).

Study design

Design

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

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	23-04-2012
Enrollment:	3
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Lyrica
Generic name:	Pregabalin
Registration:	Yes - NL outside intended use

Ethics review

Approved WMO Date:	24-06-2011
Application type:	First submission
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	28-07-2011
Application type:	First submission
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	06-12-2011
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	01-02-2012
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	22-03-2012
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	03-05-2012

Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	04-06-2012
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	25-07-2012
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	24-09-2012
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	28-09-2012
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	04-12-2012
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	16-05-2014
Application type:	Amendment
Review commission:	METOPP: Medisch Ethische Toetsing Onderzoek bij Patienten en Proefpersonen (Tilburg)
Approved WMO Date:	10-06-2014
Application type:	Amendment
Review commission:	METOPP: Medisch Ethische Toetsing Onderzoek bij Patienten en Proefpersonen (Tilburg)
Approved WMO Date:	28-07-2015
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)

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	EUCTR2010-020852-79-NL
CCMO	NL36774.028.11