A Double-Blind, Placebo-Controlled, Parallel-Group, Multicenter Study of the Efficacy and Safety of Pregabalin as Adjunctive Therapy in Children 1 Month through <4 Years of Age with Partial Onset Seizures.

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Primary Efficacy Objective* The primary objective of this study is to evaluate the efficacy of two dose levels of pregabalin compared to placebo as an adjunctive treatment in reducing the frequency of partial onset seizures in pediatric subjects 1...

Ethical review	Approved WMO
Status	Will not start
Health condition type	Neurological disorders NEC
Study type	Interventional

Summary

ID

NL-OMON40899

Source
ToetsingOnline

Brief title
Daisy

Condition

- Neurological disorders NEC

Synonym
partial onset seizures

Research involving

Human

Sponsors and support

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

Intervention

Keyword: partial onset epilepsy, pregabalin, randomized trial

Outcome measures

Primary outcome

Primary Efficacy Endpoint

* The primary endpoint will be the log transformed double blind 24 hr seizure rate for all partial onset seizures collected at Visit 6 (48 hour Video EEG assessment phase) during the double blind phase as determined by the central reader. This 24 hour seizure rate will be calculated as follows for the double blind phase:

* When the log transformation is used, the quantity is added to the double blind 24 hr EEG seizure rate for all subjects to account for any possible "0" seizure incidence. This will result in the following primary efficacy measure: loge (double blind 24 hr EEG seizure rate +). Results will be reported as *percent change in seizures* relative to placebo. For example, a difference between one of the pregabalin doses and placebo of 0.400 on the log transformed scale for the double blind 24 hr seizure rate, corresponding to a 33% reduction in the double blind 24 hour EEG seizure rate of the pregabalin group from the placebo group (ie, 100%*[exp 0.400 1]= 33%]).

* A minimum of 24 hours of evaluable Video EEG will be required to utilize the EEG. In cases where there is less than 24 hours of evaluable Video EEG, the seizure rate will be set to missing.

* The baseline 24 hour EEG seizure rate will be calculated in the same way.

Secondary outcome

Secondary Efficacy Endpoint

* Responder Rate, defined as subjects who have a *50% reduction from baseline in partial seizure rate during the double blind 48 hour EEG period. Subjects meeting this criterion will be considered responders.

Safety Endpoints

* The evaluation of safety will include adverse event (AE) data (occurrence, nature, intensity, and relationship to study drug), assessment of clinical laboratory data and the results of physical examinations, vital signs, neurological examinations and electrocardiograms (ECGs).

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 management of their seizures. In addition, children with epilepsy often suffer from impaired academic performance, with 55% functioning below their grade level and an additional 16% significantly behind in educational training.1 Children with epilepsy also have a higher likelihood of developing behavioral difficulties, which may persist into adulthood.2 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 well tolerated, is needed.
Pregabalin is approved in more than 100 countries, with indications summarized below for the United States (US), European Union (EU), and Japan (JP). In the US, pregabalin is indicated for the adjunctive therapy for adult patients with partial onset seizures. In addition, pregabalin is indicated for the management of neuropathic pain associated with diabetic peripheral neuropathy, post herpetic neuralgia, and fibromyalgia and neuropathic pain associated with spinal cord injury. In the EU, pregabalin is indicated as adjunctive therapy in adults with partial seizures with or without secondary generalization. In addition, pregabalin is indicated for the treatment of peripheral and central neuropathic pain in adults and for generalized anxiety disorder in adults. In Japan, pregabalin is indicated for the treatment of peripheral neuropathic pain and fibromyalgia. 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 3 times daily (TID). The most common adverse effects reported with pregabalin in placebo controlled adjunctive trials in adults with partial onset seizures were dizziness (32%) and somnolence (22%). Since initial market approval of Lyrica* in 2004 through the first quarter of 2012, it is estimated that more than 15,900,000 patient years of exposure have accumulated worldwide.
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 to address post approval commitments to US and EU regulatory authorities.

Study objective

Primary Efficacy Objective
* The primary objective of this study is to evaluate the efficacy of two dose levels of pregabalin compared to placebo as an adjunctive treatment in reducing the frequency of partial onset seizures in pediatric subjects 1 month through <4 years of age.
Secondary Efficacy Objective
* To evaluate the efficacy of pregabalin compared with placebo on the frequency of partial onset seizures as determined by responder rate in pediatric subjects 1 month through <4 years of age.
* To assess the safety and tolerability of pregabalin in pediatric subjects 1 month through <4 years of age with partial onset seizures.

Study design

Study Design:
Study A0081042 is a double blind, placebo controlled, randomized, parallel group, multicenter study to evaluate the efficacy of two dose levels of pregabalin compared to placebo administered TID as adjunctive therapy in pediatric subjects 1 month (44 weeks gestational age) to <4 years of age with partial onset seizures with or without secondary generalization.
Randomization will be stratified by subject age (Stratum 1: <1 year of age;

Stratum 2: 1 2 years of age; Stratum 3: >2 years of age). Subjects in each age stratum within site will be randomized to either placebo or 1 of 2 fixed doses of pregabalin divided TID, Dose Level 1: pregabalin 7 mg/kg/day [6 mg/kg/day for subjects 1 to 3 months of age] or Dose Level 2: pregabalin 14 mg/kg/day [12 mg/kg/day for subjects 1 to 3 months of age] in a 2:2:1 ratio. Every reasonable effort will be made to enroll a minimum of 10 subjects in each of the 3 age strata.
The study is composed of 4 phases:
* Video Electroencephalographic (EEG) baseline phase with a target minimum of 48 hours. To ensure that the target minimum of 48 hours of Video EEG is obtained, the total duration of the Video EEG baseline phase will be up to 72 hours.
* 5 day double blind dose escalation phase.
* 9 day double blind fixed dose treatment phase, which includes a Video EEG evaluation over the final 3 days at the end of this 9 day phase with a target minimum of 48 hours and a total recording duration of up to 72 hours. For subjects who successfully complete the target 48 hour Video EEG or must terminate the Video EEG recording before the end of this 9 day phase, fixed dosing will continue until beginning the taper phase.
* 7 day double blind taper phase.
The total double blind treatment phase is 21 days.
Every reasonable attempt should be made to obtain the minimum target Video EEG recording of 48 hours, which may require up to 72 hours to obtain. Recognizing the inherent challenges in Video EEG monitoring of pediatric subjects with epilepsy it is expected that the target minimum 48 hour Video EEG recording may not be achievable in all cases. In the clinical investigator*s opinion, should circumstances (eg, clinical care, child behavior, consent, etc.) mandate a Video EEG monitoring period less than 48 hours for a given subject, please contact the study clinician to review the subject*s clinical circumstances and document reasons for not achieving the target minimum duration.
Subjects who complete the treatment phases of this study through Visit 7 and enter the double blind taper phase will be eligible for screening into Protocol A0081106, a 1 year open label safety study (Please refer to Section 1.5 Study A0081106: 1 Year Open Label Safety Study of Pregabalin for more details). Subjects who participated in study A0081042 through Visit 7 will be considered to have completed the study.
In certain instances subjects who require withdrawal from this study may still be eligible for screening and entry into the long term safety study A0081106. Subjects who do not meet the inclusion criteria of at least 2 partial seizure during the 48 hour baseline Video EEG may still be eligible for screening for A0081106. Subjects who have completed the dose escalation phase and received at least one dose during the fixed dose phase may also be eligible for screening for Protocol A0081106. For example, subjects who withdrew due to poor tolerability or lack of efficacy may be considered. Such cases should be reviewed with the Pfizer study clinician to determine further eligibility.

Intervention

Subjects who complete the baseline phase and meet the eligibility criteria will be randomized in a double blind manner at Visit 3 to a fixed dose of either of the following. Study drug will be administered TID in equally divided doses:
* Placebo.
* Level 1: pregabalin 7.0 mg/kg/day [6 mg/kg/day for subjects 1 to 3 months of age].
* Level 2: pregabalin 14.0 mg/kg/day [12 mg/kg/day for subjects 1 to 3 months of age].

Study burden and risks

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

Other side effects that have been reported in at least 2% of subjects (2 in 100) are described in order of decreasing frequency below:
Headache, weight gain, feeling tired, nausea, fluid retention, dry mouth, blurry vision, constipation, nose and throat inflammation, diarrhea, chest infection, flu, difficulty sleeping, difficulty paying attention, difficulty with balance, back pain, joint pain, vomiting, depression, shakiness, euphoria (an unrealistic feeling of wellbeing), bladder infection, pain, sinus inflammation, feeling sedated, difficulty coordinating movements, feeling a sensation of motion, forgetfulness, increased appetite, rash, double vision, muscle spasms, decreased sensation, bronchitis, falls, anxiety, abnormal coordination, chest pain, pins and needles sensation, confusion, indigestion, decreased energy.

Serious, possibly life-threatening, side effects have been reported in past pregabalin studies. No serious side effect has happened in more than 1% of the 17,727 subjects (1 in 100) treated with pregabalin. Serious side effects that have been reported in at least 0.2% of subjects (2 in 1000) in order of decreasing frequency include pneumonia, chest pain, fall, heart attack, cellulitis, congestive heart failure and stroke.

Based on combined clinical trial data from 11 different anti-epileptic drugs including pregabalin, an increased risk of suicidal thoughts and behavior was identified in a very small number of people, about 1 in 500, taking one of these drugs.
In studies where subjects took pregabalin or placebo (a sugar pill with no medication), a higher proportion of subjects receiving pregabalin reported blurred vision than subjects treated with placebo. Eye testing by eye doctors in these studies suggested that pregabalin might be associated with some difficulty in reading small print or in peripheral vision compared to placebo. These effects on the eye were present for a short time and did not happen more

often or at more severe rates when pregabalin was administered over longer periods of time.

Pregabalin may cause serious allergic reactions.
There have been reports of congestive heart failure (a type of heart condition) in some patients receiving pregabalin since it has been marketed. Symptoms of congestive heart failure include: Shortness of breath, persistent coughing or wheezing, swelling in the feet, ankles, legs or abdomen, weight gain (edema), tiredness, fatigue. Worsening or new edema should be discussed with your doctor.
Two year cancer studies were conducted in rats and mice. At doses similar to the highest recommended dose in humans, an increased number of cancerous blood vessel tumors were observed in pregabalin treated mice. These findings did not occur in other species and the relevance of these findings to humans is unknown. Additional studies were conducted to understand how these blood vessel tumors formed. The results suggest that the action responsible for tumor formation may be specific to mice. This kind of blood vessel tumor has not been reported in pregabalin IR-treated patients; however, the length of treatment may not have been long enough to fully assess this.

Skin changes ranging from areas of reddening of skin to areas of dead skin were observed in rats and monkeys and were located mainly on the tail in most animals. They usually healed before the study ended. The causes of the skin changes remain unknown.

Placebo Risk:
Certain research participants in this study will receive a placebo. Taking a placebo may be similar to not taking any medication.

Procedure Risk:
Risks and possible discomforts your child might experience from the study procedures include:
* Blood draws: A blood draw may cause faintness, inflammation of the vein, pain, bruising, or bleeding at the site of puncture. There is also a slight chance of infection.
* Intravenous Catheter: The use of an intravenous (IV) catheter may cause pain, bruising, clotting, bleeding, leakage of drug solution, and possibly infection at the catheter site.
* ECG: The risks from an ECG can include skin irritation and a rash from the gel that is used or from wearing or removing the patches. The patches detect electrical impulses produced by the heart. No electricity passes through the body from the machine and there is no danger of getting an electrical shock.
* EEG: The risks from an EEG can include skin irritations and a rash from the gel that is used or from wearing or removing the patches.
* CT Scans: A CT scan exposes your child to a small dose of radiation.
* Contrast dye for CT scans: Contrast dye is usually injected when a CT scan is performed and may cause the subject to get a metallic taste in their mouth,

feel warm and rarely, experience nausea or vomiting. The contrast dye may cause pain or burning when it is injected, and may worsen kidney function in people who already have kidney disease or who are dehydrated (have not had enough liquids that day). The contrast dye may also cause an allergic reaction, which could be severe and life-threatening.
* MRI: There are risks from an MRI if the subject has one of the following: an artificial heart valve, pacemaker, metal plate, pin, or other metallic objects in your child*s body (including gun shot or shrapnel). MRI examinations release radio waves, which are very noisy. Although radio and magnetic waves used in MRI examinations are not associated with any known side effects, long term effects still remain undetermined. The subject may experience brief claustrophobia (discomfort, fatigue or fear as a result of being in a small, enclosed space) during the MRI procedure. If this happens, the subject may be given medication (or anesthetics) in order to lie still in a small space or you/your child may request to end participation in the MRI procedure. These drugs may affect people differently and could have possible side effects. Some side effects of most commonly used drugs include: local reactions at the site of injection, dry mouth, constipation, nausea, vomiting, vision disturbances, cardiovascular (high/low heart rate, high/low blood pressure) and respiratory disturbances, muscle spasms, tremor, agitation, confusion, headache, dizziness, allergic reactions. However, serious complications and side effects are not common, especially in people who are generally healthy.

Other Risks
Since pregabalin is investigational when taken alone or in combination with other medications, there may be other risks that are unknown.

Contacts

Public
Pfizer

Eastern Point Road MS 8260-2238
Groton 06340
US
Scientific
Pfizer

Eastern Point Road MS 8260-2238
Groton 06340
US

Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Children (2-11 years)

Inclusion criteria

1. Evidence of a personally signed and dated informed consent document indicating that the parent(s)/guardian(s) have been informed of all pertinent aspects of the study. When there are 2 parents, or 2 guardians, consent should be obtained from both of the child*s parents/guardians if present at the meeting where the informed consent document is signed.
2. Subjects and Parent(s)/guardian(s)/caregiver(s) who are willing and able to comply with scheduled visits, treatment plan, laboratory tests, and other study procedures.
3. Male and female subjects, 1 month (44 weeks gestational age) through <4 years of age inclusive on the date of the Screening Visit with a diagnosis of epilepsy with seizures classified as simple partial, complex partial or partial becoming secondarily generalized, according to the International League Against Epilepsy (ILAE 20103 see Appendix 1) Diagnosis must be established by:
* Subject*s seizure history (eg, description of seizures excluding confounding disorders such as pseudoseizures etc), family history and neurological exam.
* Subjects must have previously had a contrast enhanced computed tomography (CT) or magnetic resonance imaging (MRI) scan of the brain and EEG testing. Results must be consistent with the diagnosis of focal onset epilepsy and must demonstrate that no abnormality is likely to be progressive .
* In the event that a CT or MRI scan is needed, it should be performed as soon as possible after Visit 1 if it cannot be performed the day of this visit and must be completed and reviewed prior to randomization.
4. Currently receiving a stable dose of 1 to 3 antiepileptic drugs (stable within 7 days prior to screening). Benzodiazepine medication used on a regular basis at a stable dosage will be considered 1 of the concurrent antiepileptic treatments, Vagus Nerve Stimulator when present will also be considered 1 of the concurrent antiepileptic treatments.
5. A 12 lead ECG at screening without clinically significant abnormal findings as determined by the investigator. Potentially clinically significant abnormal findings will be reviewed by a pediatric cardiologist at the central ECG laboratory.
6. Subjects must have had at least 3 observed seizures in the month prior to screening.
7. Subjects must have at least 2 partial onset seizures as determined by the investigator or designee during the 48 hour baseline Video EEG phase.

Exclusion criteria

1. Primary generalized seizures (including in the setting of co existing partial onset seizures) which may 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.
4. Exacerbation of partial onset seizures due to fever occurring within 60 days of screening.
5. Status epilepticus within 1 year prior to screening.
6. Seizures related to acute medical illness.
7. Any change in AED regimen (type of medication or dose) within 7 days of the Screening Visit or during the Baseline Phase.
8. Progressive structural central nervous sytem (CNS) lesion or a progressive encephalopathy.
9. Progressive errors of metabolism.
10. 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). Subjects who experienced neonatal hyperbilirubinemia may be included after consulting with the study clinician.
11. Estimated creatinine clearance (ClCR) <80 mL/min/1.73 m2 (see Section 7.4.1).
12. Subjects whose parents/caregivers are investigational site staff members directly involved in the conduct of the trial or otherwise supervised by the Investigator.
13. Participation in other studies involving investigational drug(s) (Phases 1 4) within 30 days before the current study begins and/or during study participation.
14. Other severe acute or chronic medical, psychiatric condition or laboratory abnormality that may increase the risk associated with study participation or investigational product administration or may interfere with the interpretation of the study results or in the judgment of the investigator, would make the subject inappropriate for entry into this study. Patients with complex medical histories, including genetic or chromosomal syndromes, should be discussed with the study clinician prior to screening.
15. The concomitant use of gabapentin, felbamate, and vigabatrin is prohibited.
16. Previous treatment of epilepsy with pregabalin.
17. Weight >30.0 kg.

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:	Will not start
Enrollment:	1
Type:	Anticipated

Medical products/devices used

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

Ethics review

Approved WMO Date:	13-03-2014
Application type:	First submission
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	22-07-2014
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	24-09-2014
Application type:	First submission

Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	22-06-2016
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	EUCTR2013□003420□37-NL
CCMO	NL48000.028.14