RANDOMISED DOUBLE BLIND 12-MONTH STUDY OF PREGABALINE FOR PATIENTS WITH RESTLESS LEGS

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Primary• To assess the efficacy of a fixed dose of pregabalin to placebo during the first12-week treatment period in subjects with RLS.• To compare the rate of augmentation of a fixed dose of pregabalin to 2 fixed doses ofpramipexole over 9 or 12...

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Movement disorders (incl parkinsonism)
Study type	Interventional

Summary

ID

NL-OMON35592

Source
ToetsingOnline

Brief title
A0081186

Condition

- Movement disorders (incl parkinsonism)

Synonym
restless legs syndrome

Research involving
Human

Sponsors and support

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

Intervention

Keyword: augmentation, lyrica, pregabaline, restless legs syndrome (RLS)

Outcome measures

Primary outcome

Changes from baseline in RLS symptom severity using the International Restless

Leg

Group Rating Scale (IRLS) total score for efficacy assessment;

• The proportion of subjects responding to treatment using the Clinical Global

Impression - Improvement (CGI-I) scale for efficacy assessment. Responders are

defined as those who report CGI-I scores of *very much improved* or *much

improved*;

Rate of augmentation over 9 or 12 months as determined by the centralized

Adjudication Board by reviewing all cases that passed a set of assessment for

potential augmentation. The assessment will rely upon a set of criteria

including:

1. The Structured Interview for Diagnosis of Augmentation during RLS treatment

(SIDA-RLS) based on augmentation diagnostic criteria established by Allen

et al, in 2003; or

2. Augmentation Severity Scale (ASRS); or

3. Clinical judgment that augmentation might be present.

Secondary outcome

Severity of augmentation symptoms using ASRS total score;

• Clinical Global Impressions - Severity (CGI-S);

• Medical Outcomes Study - Sleep Scale (MOS - SS);

• Subjective Sleep Questionnaire (SSQ);

• RLS-Quality of Life Scale (RLS-QoL);

• Medical Outcomes Study - Short Form 36 (SF-36);

• Limb pain rating using a visual analog scale (Limb Pain - VAS);

• RLS-Next Day Impact Scale (RLS-NDI);

• Work productivity and Activity Impairment questionnaire (WPAI:SHP):

• Profile of Moods scale (POMS)

Study description

Background summary

Restless Legs Syndrome (RLS) is a common neurological disorder characterized by the
presence of an urge to move the legs, usually accompanied by dysesthesias. Symptoms
which occur primarily in the evening or at night can be alleviated by movement, and are
exacerbated by rest. Research evidence supports the involvement of dopaminergic
mechanisms in the pathogenesis of this disorder, and several dopaminergic agents (DA),
including dopamine receptor agonists, have shown to be effective in clinical studies.
The treatment of choice is considered to be based on dopaminergic substances.
However, dopaminergic drugs have potential limitations including, augmentation, lack of
sustaining efficacy in some patients and intolerability. Clinical evidence suggests a new
class of compound, alpha-2-delta calcium channel ligands, ie, gabapentin and pregabalin,
may exhibit a better risk/benefit ratio in treating RLS as compared to DAs.
Pregabalin (Lyrica®) has been approved for the treatment of neuropathic pain and adjunctive
treatment for epilepsy, and recently for fibromyalgia in the US. In some European countries,
in addition to neuropathic pain and epilepsy, pregabalin has also been approved for
management of generalized anxiety disorder.

Pramipexole is one of the two dopamine agonists approved for treating RLS in the US and
EU and is the most frequently used and studied agent in treating RLS. Based on these
criteria, pramipexole is selected as the comparator for this study.

Study objective

Primary
• To assess the efficacy of a fixed dose of pregabalin to placebo during the first
12-week treatment period in subjects with RLS.
• To compare the rate of augmentation of a fixed dose of pregabalin to 2 fixed doses of
pramipexole over 9 or 12 months in subjects with RLS.
Secondary
• To assess the comparability of efficacy of a fixed dose of pregabalin with 2 fixed
doses of pramipexole in treating symptoms of RLS during the first 12 weeks and beyond, through the end of the study,
the severity of augmentation associated with pregabaline or pramipexole treatment,
the tolerability and safety of pregabalin and pramipexole treatment over 1 yr,
the impact of pregabalin and pramipexole treatment on subjective sleep parameters over 1 yr,
the impact of pregabalin and pramipexole treatment on next day impact over 1 yr,
the impact of pregabalin and pramipexole treatment on mood as comparator to placebo during the first 12 wks,
the impact of pregabalin and pramipexole treatment on quality of life over 1 yr,
the impact of pregabalin and pramipexole treatment on limb pain during the firts 12 wks,
the impact of pregabalin and pramipexole treatment on work productivity and activity impairment over 1 yr.

Study design

This is a fixed-dose, randomized, 12-week placebo-controlled, 52-week pramipexole controlled,
double-blind study to assess the rates of augmentation, efficacy and safety of pregabalin and pramipexole in subjects with moderate to severe idiopathic RLS.
Study scheme see page 3 of the protocol

Intervention

Following a running-in period, the participants will be divided into 4 groups.
One group will receive pregabaline (300 mg per day), 2 groups will receive

pramipexol (0.25 or 0.5 mg per day) and 1 group will receive a placebo. These groups will be assigned by means of a lottery. Neither the participants nor the study doctor can influence the outcome of the lottery and neither of you will know which group you have been assigned to. After 12 weeks the treatment with placebo will be stopped and the patients from this group will receive pregabaline or one of the two doses of pramipexol for the remaining 40 weeks. The other groups will continue to receive their original study medicine.
The study medicine is used every day, 1 - 3 hours before going to sleep (orally).

Study burden and risks

Subjects are to be advised to take the study medication while at home and remain at
home for the rest of the evening.
• Subjects are to be instructed to avoid consuming alcohol
Subjects are to be cautioned against driving a motor vehicle or operating heavy machinery within 24 hours after the first dose of study medication has been administered but should maintain their normal daily routine otherwise. If a subject
experiences dizziness or somnolence during the trial, then driving a motor vehicle or
operating heavy machinery should be avoided until symptoms resolve.
• Women of childbearing potential must use 2 reliable methods of contraception or
practice abstinence during the study period or be surgically sterilized.
• Donation of a unit of blood or plasma during the study is prohibited

Contacts

Public
Pfizer

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NY 10017 New York
US
Scientific
Pfizer

235 East 42nd street
NY 10017 New York
US

Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

1. Diagnosis of RLS is to be made by a Physician with experience and/or training in RLS. Idiopathic RLS with the presence of all four clinical manifestations of
RLS:
• Urge to move the legs usually with dysesthesias: An urge to move the legs usually accompanied or caused by uncomfortable and unpleasant sensations in the legs. (Sometimes the urge to move is present without the uncomfortable ensations and sometimes the arms or other body parts are involved in addition to the legs);
• Onset or exacerbation with rest: The urge to move or unpleasant sensations begin or worsen during periods of rest or inactivity such as lying or sitting;
• Relief with movement: The urge to move or unpleasant sensations are partially or totally relieved by movements, such as walking or stretching, at least as long as the activity continues;
• Circadian pattern: The urge to move or unpleasant sensations are worse in the evening or night than during the day or only occur in the evening or night (when symptoms are very severe, the worsening at night may not be noticeable but must have been previously present);
• The following instruments will be utilized to aid the diagnosis:
• Medical history and/or RLS treatment history.
• Cambridge-Hopkins Restless Legs Syndrome Short Form Diagnostic Questionnaire (RLS-SFDQ-9) - entered by the subjects.
• RLS-Clinical Diagnostic Interview (RLS CDI) - conducted and signed-off by the Investigator.
2. RLS symptoms must occur predominantly in the evening (between the hours of 17:00 to 07:00).
3. A history or the presence of RLS symptoms for at least 6 months.
4. An International Restless Leg Scale (IRLS) total score >=15 at beginning of placebo run-in (1 week prior to Baseline) and end of placebo run-in (Baseline).
5. Have >=15 nights with RLS symptoms in the month prior to Screening. Subjects receiving RLS therapy at the time of Screening are to have had >=15 nights per

month with RLS symptoms prior to initiation of this treatment. Have >=2 nights with RLS symptoms during the week of placebo run-in.
6. Both genders. Age 18 years or older.
7. Evidence of a personally signed and dated Informed Consent Document indicating that the subject (or a legally acceptable representative) has been informed of all pertinent aspects of the trial.
8. Willing and able to comply with scheduled visits, treatment plan, laboratory tests, and other trial procedures

Exclusion criteria

Subjects may not participate in the study if they meet any of the following criteria:
1. Any secondary form of RLS which is primarily attributable to other conditions, eg, end stage renal disease, iron-deficiency anemia.
2. Current augmentation due to RLS treatment, or pramipexole-caused clinically significant augmentation within 6 weeks of the Screening Visit. Clinically significant augmentation is defined as the subject experiences symptoms that are severe enough to impact the subject*s daily life and/or requires an alteration of treatment, eg, change to another class of medication.
3. Requiring regular (more than 2 times a week within 3 months of screening visit) medication treatment for daytime RLS symptoms (between the hours of 07:00 to 17:00).
4. Placebo responders as defined by a >50% improvement in RLS symptoms, ie, decrease of the total score in IRLS Scale between beginning of placebo run in (1 week prior to Baseline) and end of placebo run-in (Baseline Visits).
5. Any symptomatic neuropathies or current diagnosis of clinically relevant concomitant conditions that may confound clinical assessments of RLS and/or severe enough to disturb sleep, for example, painful leg and moving toes syndrome.
6. Clinically significant lumbar radiculopathy or central spinal stenosis by history or examination.
7. Presence of severe central nervous degenerative diseases such as Parkinson*s disease, dementia, progressive supranuclear paresthesia, multisystem atrophy, Huntington Chorea, amyotrophic lateral sclerosis, or Alzheimer*s disease.
8. History or presence of a severe sleep disorder, especially those with difficulty falling and/or staying asleep, that may confound assessments (Apnea/Hypopnea Index greater than 20 if a sleep study has been previously performed) at the Screening or Baseline Visits.
9. Use of medications likely to influence sleep architecture or motor manifestations during sleep prior to the Baseline Visit (BL) without an appropriate washout period. Refer to Appendix 1 for the list of exclusionary medications. These include neuroleptics, hypnotics, sedatives, antidepressants, anxiolytics, anticonvulsants, psychostimulantmedications, barbiturates and opioids. 10. Clinically significant liver disease, or an elevation in either bilirubin, aspartate aminotransferase (ASAT), or alanine aminotransferase (ALAT) levels >3 times the upper limit of normal value (ULN).
11. Clinically significant renal disease, or creatinine clearance level <60 mL/min esttimated by Cockroft Gault method).

12. Any other clinically significant condition (eg, cardiac dysfunction, active neoplasm, uncorrected hypothyroidism or hyperthyroidism) or laboratory assay abnormality.
13. Failure to respond positively to dopaminergic agents, gabapentin or pregabalin in treating RLS according to medical history. 14. Known hypersensitivity to any components of the trial medication or similar drugs.
15. Serum ferritin below 15µg/L.
16. Employment hours disruptive to the normal circadian sleep wake cycle such as nighttime or variable rotating shifts.
17. Suicide risk (life time) by medical history and by assessment using C-SSRS. If the subject responds *yes* to any of the C-SSRS questions and yet the subject is allowed to participate in the trial, a risk assessment narrative must be constructed by the Investigator.
18. Pregnant or lactating women, or women with child bearing potential who are not surgically sterile, two years postmenopausal, or do not practice two combined methods of medically acceptable forms of contraception.
19. Participating in other investigational drug studies or having received other investigational drugs within the previous 30 days of the Screen Visit.
20. Current or history of chronic alcohol or drug abuse within the past 12 months.

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):	29-01-2010
Enrollment:	16
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Pramipexol
Generic name:	Sifrol
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	Pregabaline
Generic name:	Lyrica
Registration:	Yes - NL outside intended use

Ethics review

Approved WMO Date:	22-07-2009
Application type:	First submission
Review commission:	IRB Amsterdam: Independent Review Board Amsterdam (Amsterdam)
Approved WMO Date:	17-09-2009
Application type:	First submission
Review commission:	IRB Amsterdam: Independent Review Board Amsterdam (Amsterdam)
Approved WMO Date:	07-10-2009
Application type:	Amendment
Review commission:	IRB Amsterdam: Independent Review Board Amsterdam (Amsterdam)
Approved WMO Date:	19-03-2010
Application type:	Amendment
Review commission:	IRB Amsterdam: Independent Review Board Amsterdam (Amsterdam)

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	EUCTR2008-005889-32-NL
CCMO	NL28102.003.09