A 24-month, Prospective, Randomized, Active-Controlled, Open-Label, Rater Blinded, Multicenter, International Study of the Prevention of Relapse Comparing Long-Acting Injectable Paliperidone Palmitate to Treatment as Usual with Oral Antipsychotics Monotherapy in Adults With Schizophrenia.

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Primary ObjectivesThe primary objective is to assess the efficacy (primarily through time to relapse) of long-acting injectable (LAI) paliperidone palmitate compared to treatment as usual with orally administered antipsychotics in monotherapy over…

Ethical review	Not approved
Status	Will not start
Health condition type	Schizophrenia and other psychotic disorders
Study type	Interventional

Summary

ID

NL-OMON32671

Source
ToetsingOnline

Brief title
geen verkorte titel

Condition

- Schizophrenia and other psychotic disorders

Synonym
disambiguation; madness

Research involving
Human

Sponsors and support

Primary sponsor: Janssen-Cilag
Source(s) of monetary or material Support: Janssen-Cilag B.V.

Intervention

Keyword: Antipsychotics, Schizophrenia

Outcome measures

Primary outcome

The primary endpoint of the 24-month treatment phase will be the time to relapse. The relapse criteria are based on criteria reported by Csernansky et al.40, and have been employed in several previous trials. Relapse in the current study is defined by any one of the following:

•Psychiatric hospitalization; or

•An increase in the level of psychiatric care (e.g., significant crisis intervention needed to avert hospitalization, clinically notable increases in the frequency or intensity of patient contact required to maintain outpatient status) and an increase of 25% from baseline in the total score on the PANSS (or an increase of 10 points if the base-line score was 40 or less); or

•Deliberate self-injury; or

•Suicidal or homicidal ideation that was clinically significant in the investigator*s judgment; or

•Violent behavior resulting in clinically significant injury to another person

or property damage; or

•Substantial clinical deterioration, defined as a change score of 6 (*much worse*) or 7 (*very much worse*) on the Clinical Global Impressions Scale; or

•The required dose of the antipsychotic exceeds the maximum approved dose.

Key efficacy evaluations will include the following:

•Rate of patients with relapse at the 24-month endpoint;

•Rate of patients with psychiatric hospitalizations;

•Psychiatric hospitalizations (total number and mean duration);

•Response rate using PANSS and changes versus baseline in total PANSS and PANSS subscales;

•Changes from baseline in levels of personal and social functioning measured using the PSP scale;

•Global severity of illness overall score and changes measured using the CGI-S and CGI-C scales;

•Measures of subject's mental health (SF-36; EQ5D) and well-being (SWN);

•Subject treatment satisfaction (TSQM) and physician treatment satisfaction (7-point categorical scale).

Secondary outcome

SAFETY EVALUATIONS

•A physical examination will be performed at screening and at endpoint;

•Vital signs and weight will be measured at screening, at all visits during the 24-month treatment phase, and upon early withdrawal;

•Height will be measured at screening;

•A urine pregnancy test (for females of childbearing potential) will be

performed at screening and at endpoint;

•Extrapyramidal symptom rating scales (AIMS, SAS, and BARS) will be assessed at screening, and at Visits 2-4 and Visit 8-13 during the 24-month treatment phase and at endpoint;

•(S)AE .

OTHER EVALUATIONS

•Health/social care utilization measured through HRUQ;

•Measures of alcohol and substance use (CRAUS; CRSUS);

•Measures of subject*s suicidality (ISST).

Study description

Background summary

Paliperidone palmitate (R092670) is the palmitate ester prodrug of paliperidone (9 hydroxy risperidone, R076477), a selective, monoaminergic antagonist that exhibits the characteristic dopamine type 2 (D2) and serotonin (5 hydroxytryptamine [5-HT]) type 2A (5HT2A) antagonism of the newer, or second generation, antipsychotic drugs. Paliperidone is the major active metabolite of risperidone and is a racemic mixture of the enantiomers R078543(+) and R078544(-). Paliperidone palmitate is being developed as a long acting intramuscular (i.m.) injectable aqueous suspension formulation for the treatment of schizophrenia.

Study objective

Primary Objectives
The primary objective is to assess the efficacy (primarily through time to relapse) of long-acting injectable (LAI) paliperidone palmitate compared to treatment as usual with orally administered antipsychotics in monotherapy over 24 months in the treatment of recently diagnosed (1-5 years since diagnosis) schizophrenia.
The relapse criteria (see Section 9.2.2.1.) are based on criteria reported by Csernansky et al.40, and have been employed in several previous studies.

Secondary Objectives
The secondary objectives are to examine additional efficacy, safety and tolerability of paliperidone palmitate compared with treatment as usual with a variety of orally administered antipsychotic medications in monotherapy, until relapse or over maximally 24 months (whichever comes first), in subjects with recently diagnosed schizophrenia, and to compare the effect of paliperidone palmitate to treatment as usual with orally administered antipsychotic medications in monotherapy on clinically important domains.

Study design

This is a randomized, open-label, rater-blinded, active-controlled, parallel-group, multicenter, prospective international study of paliperidone palmitate versus treatment as usual with oral antipsychotic agents in monotherapy in the prevention of relapse. Approximately 766 subjects, of both genders and between 18 and 65 years of age, who have a Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) diagnosis of recently diagnosed (1 to 5 years since diagnosis) schizophrenia and suffering from a schizophrenic relapse will be enrolled. The oral comparator arm consists of 6 oral antipsychotics, i.e. oral haloperidol and the 5 atypical antipsychotics paliperidone ER, risperidone, olanzapine, quetiapine and aripiprazole.
The study consists of a 2-week initial acute oral treatment phase, followed by a core treatment phase until relapse or up to maximally 24 months, whichever comes first. Only subjects fulfilling the response criteria at the end of the 2 week initial acute oral treatment phase, will enter the subsequent 24-month treatment phase.

Intervention

Upon meeting the response criteria, subjects will enter the 24-month treatment phase for initiation of paliperidone palmitate or continuation of oral antipsychotic therapy, in an open-label, rater-blinded fashion. This will be obtained by appointing blinded raters, who are not involved in any other aspect of the study. The blinded raters will be responsible for administering the PANSS, the PSP, the CGI-S and the CGI-C. The investigator will be responsible for all other assessments and the treatments. The investigator will therefore also decide whether a dose change is required.
Subjects randomized to paliperidone palmitate will receive paliperidone palmitate deltoid injections in alternate arms at a dose of 150 mg eq. on Day 1 and a dose of 100 mg eq. on Day 8, followed by 75 mg eq. on Day 38 in either the deltoid or gluteal muscle, and clinically-defined doses in a dose range of 25 to 150 mg eq. in either the deltoid or the gluteal muscle thereafter.
Subjects randomized to treatment with oral medications will have this oral antipsychotic medication continued as the randomization-defined treatment at a dose defined by the investigator.

Subjects randomized to treatment with paliperidone palmitate will be treated with paliperidone ER (INVEGA*). Flexible dosing will be applied within the approved dose range of 3 to 12 mg once daily in the morning. Subjects entering the initial acute oral treatment phase on oral antipsychotic medication and randomized to treatment with paliperidone palmitate will have their oral antipsychotic medication tapered off over a maximum of 7 days and replaced with oral paliperidone ER (INVEGA). This initial acute oral treatment phase includes tolerability testing of paliperidone. A review of the oral RISPERDAL and RISPERDAL CONSTA safety databases has revealed some cases of allergic and hypersensitivity reactions. Since paliperidone palmitate is a long acting medication with a half-life of 20 to 30 days, it is important to identify those subjects who may have either a severe tolerability problem or an allergic reaction before injection. Only subjects who demonstrate an ability to tolerate the drug as judged by the treating physician, will be eligible for treatment with paliperidone palmitate. The first dose of paliperidone ER will be given on the day of screening if the screening visit is performed in the morning of that day, otherwise in the morning of the next day.
Subjects randomized to the oral antipsychotics arm will be treated with one of the 6 oral antipsychotics (paliperidone ER, risperidone, olanzapine, quetiapine, aripiprazole, or oral haloperidol) as prescribed by the investigator as clinically indicated. Subjects entering the initial acute oral treatment phase on oral antipsychotic medication and randomized to treatment with oral antipsychotics will have their previous oral antipsychotic medication tapered off over a maximum of 7 days and replaced with the newly selected oral antipsychotic

Study burden and risks

Burden:
1. 15 visits to site during 2 years
2. Efficacy evaluation through PANSS and PSP (blinded rater)
2. Safety evaluation
3. Health and well-beeing questionnaires
Risks:
1. Adverse Events Paliperidone Palmitate or Oral Antipsychotic
2. Unknown risks
While the subject is participating in this study, the studyteam will follow-up on his condition very closely. The subject may benifit from the health information provided to him/her as a result of study procedures.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

• Man or woman between 18 and 65 years of age, inclusive
• The subject has a current diagnosis of schizophrenia according to DSM-IV, and has been recently diagnosed, i.e. between 1 and 5 years before screening, and was receiving antipsychotics in the past;
• The subject has a history of two or more relapses requiring psychiatric hospitalization in the preceding 24 months, which may include the current acute episode. Daytime hospitalization is acceptable in those countries where this reflects standard of care in acutely ill patients. In countries where hospitalization for relapse is not clinical standard, the requirement for hospitalization is not required;
• Subject must be experiencing at screening an acute schizophrenic episode with a PANSS total score at screening between 70 and 120, inclusive;
• The subjects may benefit from a switch of antipsychotic medication to either paliperidone palmitate or one of the oral antipsychotics used in this study;
• Otherwise healthy on the basis of physical examination, medical history and vital signs performed at screening. If there are abnormalities, they must be consistent with the underlying illness in the study population.
• Woman are not pregnant; must not get pregnant
• Subjects must be willing and able to fill out self-administered questionnaires;

• Willing/able to adhere to the prohibitions and restrictions specified in this protocol;
• The subject is cooperative and reliable, and agrees to receive regular injections and complete all aspects of the protocol;
• Subjects must have signed an informed consent document indicating that they understand the purpose of and procedures required for the study and are willing to participate in the study.

Exclusion criteria

•The subject*s psychiatric diagnosis is due to direct pharmacological effects of a substance (e.g., a drug of abuse or medication) or a general medical condition (e.g., clinically notable hypothyroidism);
•First antipsychotic treatment ever;
•Subject cannot be treated with an atypical oral antipsychotic (except oral clozapine) or oral haloperidol in monotherapy according to the investigator;
•The subject is treatment resistant in the judgment of the investigator and/or currently (i.e., within the last 3 months) treated with clozapine;
•The subject meets the DSM-IV definition of substance dependence (except for nicotine and caffeine) within 6 months prior to entry; subjects with current substance use or abuse, with the exception of intravenous drug use, will be allowed to enroll;
•Known allergies, hypersensitivity, or intolerance to risperidone or paliperidone or its excipients
•Any condition that, in the opinion of the investigator, would compromise the well-being of the subject or the study or prevent the subjects from meeting or performing study requirements;
•The subject has received treatment with a long-acting injectable antipsychotic within three injection cycles prior to screening;
•The subject has begun a psychotherapy program within the two months preceding the treatment phase baseline. Psychosocial treatment is not considered psychotherapy;
•The subject received an investigational drug or used an investigational medical device within 60 days before the planned start of treatment, or has participated in more than one investigational drug trial in the past 12 months, or has planned use of other investigational drugs during the time frame of the trial, or is currently enrolled in an investigational study;
•The subject has evidence of clinically significant hepatic, renal, cardiac, vascular, pulmonary, gastrointestinal, endocrine, neurologic, hematologic, rheumatologic, psychiatric, or metabolic disturbances in the past 6 months (as determined by medical history, clinical laboratory or ECG results, or physical examination) that would increase the risk associated with taking study medication or would confound the interpretation of the study;
•Subjects with a narrowing or blockage of their gastrointestinal tract;
•Inability to swallow the study medication whole with the aid of water (subjects may not chew, divide, dissolve, or crush the Paliperidone ER study medication, if applicable, as this may affect the release profile);
•Contraindications, warnings and precautions for oral antipsychotics used in this study apply according to local Summaries of Product Characteristics (SmPCs);
•History or current symptoms of tardive dyskinesia;

•History of neuroleptic malignant syndrome;
•Subject is involuntarily hospitalized;
•Subject is pregnant or breast-feeding;
•Employees of the investigator or study center, with direct involvement in the proposed study or other studies under the direction of that investigator or study center, as well as family members of the employees or the investigator.
•Use of disallowed therapies

Study design

Design

Study phase:	3
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Open (masking not used)
Control:	Active
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Will not start
Enrollment:	16
Type:	Anticipated

Medical products/devices used

Product type:	Medicine
Brand name:	Abilify
Generic name:	aripiprazol
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	Invega
Generic name:	Paliperidone ER
Registration:	Yes - NL intended use

Product type:	Medicine
Brand name:	Invega Sustenna (goedgekeurd door FDA in US)
Generic name:	paliperidone palmitate
Product type:	Medicine
Brand name:	Risperdal
Generic name:	Risperidon
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	Seroquel
Generic name:	quetiapine
Registration:	Yes - NL intended use

Ethics review

Approved WMO Date:	24-12-2009
Application type:	First submission
Review commission:	METIGG: Medisch Ethische Toetsingscommissie Instellingen Geestelijke Gezondheidszorg (Utrecht)
Not approved Date:	23-02-2010
Application type:	First submission
Review commission:	METIGG: Medisch Ethische Toetsingscommissie Instellingen Geestelijke Gezondheidszorg (Utrecht)

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	EUCTR2008-002247-16-NL
CCMO	NL30911.097.09