SYNOPSIS

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Name of Sponsor/Company	Janssen-Cilag GmbH, Germany
Name of Finished Product	INVEGA®
Name of Active Ingredient(s)	Paliperidone

Protocol No.: R076477SCH4026

Title of Study: The "therapeutic window" of the "atypical" antipsychotic paliperidone ER – A Positron Emission Tomography study with [18F]fallypride as the radiotracer

EudraCT Number: 2008-003340-11

Principal Investigator: Gerhard Gründer, PhD MD
Dept of Psychiatry and Psychotherapy, University of Aachen, Aachen, Germany

Publication (Reference): None.

Study Period: 20 Sep 2009 – 09 Dec 2009 (first subject in – last subject out)

Phase of Development: Phase 4

Objectives: The primary objective of this study was to compare the therapeutic D_2 receptor occupancies at time of peak and trough plasma concentrations in subchronic schizophrenic patients under stable treatment with either 6 mg or 9 mg paliperidone ER once daily, subjects under stable treatment with either 4 mg or 6 mg oral risperidone once daily and healthy controls. Therefore, it was planned to measure central D_2 receptor occupancies in relation to peak and trough drug plasma concentrations of both treatment groups compared to D2-receptor occupancies in healthy controls using positron emission tomography (PET) and to correlate with plasma drug (metabolite) concentrations at different timepoints after drug intake. Secondary, "mesolimbic selectivity" for both compounds and both treatment regimens was to be evaluated by measurements of striatal and extrastriatal regional D_2 occupancies compared to healthy controls using PET with a high affinity radiotracer ([^{18}F]fallypride), which allows quantification of striatal and extrastriatal D_2 receptors.

Methods: The study was designed as an open-label, non-randomized, monocenter, interventional study in 8 groups of patients on antipsychotic medication and one control group of healthy subjects:

Group	Subjects	Previous and current treatment	Time of PET scan
G1	3 patients	Paliperidone ER 6 mg once daily	Visit 3, 26-27 hours after last dose
G2	3 patients	Paliperidone ER 9 mg once daily	Visit 3, 26-27 hours after last dose
G3	3 patients	Risperidone ER 4 mg once daily	Visit 3, 26-27 hours after last dose
G4	3 patients	Risperidone ER 6 mg once daily	Visit 3, 26-27 hours after last dose
G5	3 patients	Paliperidone ER 6 mg once daily	Visit 3, 2-3 hours after last dose
G6	3 patients	Paliperidone ER 9 mg once daily	Visit 3, 2-3 hours after last dose
G7	3 patients	Risperidone ER 4 mg once daily	Visit 3, 2-3 hours after last dose
G8	3 patients	Risperidone ER 6 mg once daily	Visit 3, 2-3 hours after last dose
G9	10 healthy subjects	None	Visit 3

The study comprised 3 visits on 3 consecutive days. At visit 1, demographic data and baseline clinical parameters , including *Positive and Negative Syndrome Scale for Schizophrenia* (PANSS), *Clinical Global Impression - Severity* (CGI-S) and *Extrapyramidal Symptom Rating Scale* (ESRS) were assessed within the

psychiatric patients. At visit 2, pre-dose blood samples were collected (G1-G4 only) and the last (G1-G4) or last but one (G5-G8) dose of study medication prior to the PET scan was administered. At visit 3, the last dose of study medication was given (G5-G8 only) and PET scans (G1-G9) with concomitant pharmacokinetic blood sampling (G1-G8 only) were performed.

Number of Subjects (planned and analyzed): 24 patients suffering with from Schizophrenia (6 per dose level) and 10 healthy volunteers were planned to be included. Finally, one patient with schizophrenia in the treatment group G2 (paliperidone ER 9 mg) and one healthy volunteer (group G9) were enrolled and available for analysis.

Diagnosis and Main Criteria for Inclusion: (a) men or women, aged 18-50 years, with a diagnosis of schizophrenia according to DSM-IV criteria and a clinical global impression severity (CGI-S) of >2 and <5 who had been on antipsychotic medication with either paliperidone ER or oral risperidone monotherapy for at least two weeks and had been at least five days on a stable dose of either paliperidone ER or risperidone; and (b) healthy men or women, aged 18-50 years, who had been off all standard prescription drug therapy, OTC or recreational drugs for at least one week prior to participation in the study.

Test Product, Dose and Mode of Administration, Batch No.: Paliperidone ER (INVEGA®) 6 mg or 9 mg; oral administration once daily;

Reference Therapy, Dose and Mode of Administration, Batch No.: Risperidone (Risperdal®) 4 mg or 3 mg; oral administration once daily;

Duration of Treatment: 1 day (G1-4) or 2 days (G4-8) during the study

Criteria for Evaluation:
Primary endpoint: Therapeutic D_2 receptor occupancies (PET imaging of radio-tracer [18F]fallypride) at time of peak to trough plasma concentrations.
Secondary endpoint: "Mesolimbic selectivity" for both regimens and compounds evaluated by measurements of striatal and extrastriatal regional D2 occupancies using PET imaging of radiotracer [18F]fallypride.
Pharmacokinetics: concentrations of paliperidone (9-0H-risperidone) and risperidone (risperidone groups only) in plasma samples collected pre-dose and 0, 60, 120, 180 and 300 min after injection of radiotracer.
Safety: adverse events (visits 1-3); laboratory tests, vital signs, body weight, and physical examination (visit 1).

Statistical Methods: No statistical analyses were performed due to the small number of subjects studied.

RESULTS:

Conduct of the study: The study was conducted in accordance with ICH Good Clinical Practice, the principles of the Declaration of Helsinki, and the applicable local regulations.

The study was terminated prematurely due to major recruitment problems. Shortly after initiation of the study, the relevant health authorities in Germany decided that health insurances would not be required to carry the full cost of paliperidone ER treatment in the future. Consequently, most patients previously treated with paliperidone ER were switched to other antipsychotics and further recruitment of patients pre-treated with paliperidone ER could not be expected.

Disposition of subjects: Two subjects were enrolled, 1 subject on paliperidone ER 9 mg/d (referred to as "the patient" in the following sections), who was assigned to treatment group G2, and 1 healthy volunteer (referred to as "the healthy subject" in the following sections). Both subjects completed the study as planned and all study procedures were performed in these two subjects as specified in the study protocol.

Demographic and baseline characteristics: Both subjects (one patient, one healthy volunteer) met the applicable inclusion/exclusion criteria. One male subject (aged 27-years; body weight 76.9 kg, height 190 cm) with schizophrenia, paranoid subtype (DSM-IV:295.30) was assigned to the paliperidone ER 9 mg treatment group (G2). The course of the disease was classified "episodic with no inter-episode residual symptoms". The severity of the illness was rated as "moderately ill" (4 points on the 7-point CGI-S rating scale) at baseline Visit 1. PANSS total score at baseline was 61.

One female healthy subject (aged 19-years, body weight 62.0 kg, height 179 cm) was assigned to the healthy control group (G9).

Efficacy: PET imaging data were not submitted for further analysis. D2-receptor occupancies could not be calculated due to the low number of subjects in the healthy control group.

Pharmacokinetics: Measurement of plasma-concentrations were to be applied in the treatment groups only. Paliperidone plasma-concentration measured 27.5 h after the last intake of paliperidone ER in the patient assigned to G2 was 24 ng/mL.

Safety: No adverse events occurred during the treatment phase of the study.

Thirteen days after the patient completed the study (follow up period) a serious adverse event report form indicated an exacerbation of schizophrenic symptoms after illegal drug intake and the patient was temporarily transferred from an open ward to a locked ward. The patient was switched to clozapine and psychotic symptoms resolved within a few days. The patient recovered from this event without sequelae. The serious adverse event was classified by the investigator to be unrelated to study medication paliperidone ER.

STUDY LIMITATIONS: The study was prematurely terminated after inclusion of 1 subject on antipsychotic medication and 1 healthy control subject. Thus, the data obtained from both subjects were not submitted to further statistical analysis and the presentation of results is limited to a short description of individual subject characteristics and safety data.

CONCLUSION: The data collected in this prematurely terminated trial will not be applicable for scientific analysis as specified within the study protocol due to the low number of subjects included.

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