2. SYNOPSIS

Name of Sponsor: Janssen-Cilag SpA
Name of finished product: Invega
Name of active ingredient: Paliperidone
Title of study: Efficacy and Tolerability of Flexible Doses of Paliperidone ER in Symptomatic Subjects with Schizophrenia with duration of illness < 10 years
Protocol number: R076477SCH3037
EudraCT number: 2008-002384-13
Principal Investigator: Prof. Mauro Mauri Dipartimento di Psichiatria, Neurobiologia, Farmacologia e Biotecnologie - A.O. Universitaria di Pisa, [redacted] Italia
Study centre(s): n° 30 involved, n° 28 active
Study period (years): 2009-1010
Phase of development: Phase IV
Objectives: ***Primary Objective*** • explore the effect of flexible doses of extended-release (ER) Paliperidone in symptomatic subjects with schizophrenia with a duration of illness < 10 years by measuring the change in total PANSS score from baseline to endpoint. ***Secondary Objectives*** • explore tolerability, safety, efficacy, disease severity, functioning and patients' subjective experiences and attitudes toward treatments by the following measurements: • assessing the efficacy on psychotic symptoms (Positive and Negative Syndrome Scale [PANSS] subscores); • assessing the proportion of subjects improving ≥ 30% in total PANSS score from baseline to endpoint; • assessing the patients' subjective experience and attitude towards their illness and medication (Subjective Well-being Under Neuroleptic [SWN 20] and Drug Attitude Inventory [DAI 30]) • assessing disease severity (Clinical Global Impression–Severity Scale [CGI-S]); • assessing personal and social functioning (Personal and Social Performance Scale [PSP]); • assessing quality of sleep and daytime drowsiness (11-point categorical evaluation scale); • assessing side effects profiles by means of the Extrapyramidal Symptom Rating Scale (ESRS), body weight, vital signs, physical examination and adverse events (AEs).

Methodology:

Trial design/type: This was an open-label, single arm, multicentre 13-week study which was aiming to explore, tolerability, safety and efficacy of flexibly dosed Paliperidone ER in symptomatic but not highly acute subjects (total baseline PANSS score ranging from 70 to100) with schizophrenia diagnosed from less than 10 years.
Subjects were prospectively followed as outpatients in psychiatric structures (i.e.ambulatory, community center, not hospitalized in a psychiatric ward).
Symptomatic subjects were switched from their current oral antipsychotic therapy due to insufficient efficacy on symptoms (e.g. negative, positive, general) or due to side effects.
Throughout the study flexible dosing in a range of 3 to 12 mg/day could be used, to adjust the dosage of each subject as clinically indicated.
In general, the recommended Paliperidone ER dose is 6 mg once daily, but some subjects may benefit from higher or lower doses in the recommended dose range of 3 to 12 mg once daily.

Study population: Male or female patients between 18 and 45 years of age, inclusive.

Number of patients (planned and analysed):

Planned: The sample size calculations performed yielded a number of 128 patients to be enrolled.
Analysed: Enrolled patients 133. Analysed in the ITT Population 132, in the PP Population 110, in the Safety Population 132.

Diagnosis: Adult outpatients (approximately n=128) suffering from psychotic symptoms (total baseline score PANSS $\geq 70, \leq 100$) with a diagnosis of schizophrenia < 10 years.

Test product: Tablets of paliperidone ER 3, 6, 9 mg (for daily dose of 12 mg, two tablets of 6 mg).
Dose and mode of administration: Paliperidone 3 mg, 6 mg and 9 mg tablets were used.
Subjects who required a daily dose of 3 mg, 6 mg or 9 mg of Paliperidone ER took a 3 mg, 6 mg or 9 mg tablet, respectively. Subjects who required a daily dose of 12 mg of Paliperidone ER took two tablets of 6 mg together in the morning.
Medications were packed in blisters containing 7 tablets each.
Blisters containing respectively the 3 mg, 6 mg and 9 mg tablets were to be used for subjects who required a daily dose of 3 mg, 6 mg or 9 mg of Paliperidone ER.
Subjects who required a daily dose of 12 mg Paliperidone ER took two tablets of 6 mg per day.
Each subject received the amount of medication required until the next visit.

Duration of treatment: 91 (± 3) days - (13 weeks)

Statistical methods planned in the Protocol:

Two populations were considered in the statistical analysis of efficacy analysis:
Intention-to-Treat Population (ITT) included all subjects who received at least one dose of study medication.
Per-Protocol Population (PP) consisted of the subjects in the Intention-to-Treat Population who did not violate any inclusion/exclusion criteria and did not violate the protocol between baseline and study completion (major violations).

The precise reasons for excluding subjects from the Per-Protocol Population were fully defined and documented.

The primary efficacy endpoint was to explore the effect of flexible doses of extended-release (ER) Paliperidone in symptomatic subjects with schizophrenia with a duration of illness < 10 years by measuring the change in total PANSS score from baseline to study endpoint.
The null hypothesis that was tested to address the primary objective of the trial is that there is no difference between baseline and study endpoint total PANSS score.
Since the primary efficacy criterion was the change in total PANSS score measured at the end of the study (Week 13 or last post-baseline evaluation) versus baseline the one-sample t-test (or nonparametric analog Wilcoxon Signed Rank Test, if the data did not follow the normal probability distribution) was used to determine if the total PANSS mean response change from 'pre' and 'post' study treatment (paired difference t-test).
The t-test was to be conducted using SAS (version 8.2) Proc. MEANS.
The one-sample t-Test is summarized as follows:

null hypothesis (H_0):
$\mu_{pre} = \mu_{post}$,
alternative hypothesis (H_A):
$\mu_{pre} \neq \mu_{post}$,
decision rule:
reject H_0 if $|t| > t_{\alpha/2, n-1}$.

Secondary endpoints included changes from baseline to the end of the study (Week 13 or last post-baseline evaluation) in:

- Positive and Negative Syndrome Scale [PANSS] subscale scores for specific symptoms;
- proportion of subjects improving ≥ 30% in total PANSS from baseline to endpoint
- the subjective experience and attitude towards illness and medication (Subjective Well- being Under Neuroleptic [SWN 20] and Drug Attitude Inventory [DAI 30];disease severity (Clinical Global Impression–Severity Scale [CGI-S])
- personal and social functioning (Personal and Social Performance Scale [PSP]) quality of sleep and daytime drowsiness (11-point categorical evaluation scale).

Measures of central tendency, dispersion and/or frequency were reported for all Evaluation Scales (PANSS, CGI-S, PSP, DAI-30, SWN-20, ESRS) and for the sub-groups defined (different doses of extended-release Paliperidone).

A Pearson correlation coefficient was calculated to establish the link between the Evaluation Scales

(PANSS, CGI-S, PSP, DAI-30, SWN-20, ESRS).

Categorical variables (the proportion of subjects improving ≥ 30% in total PANSS from baseline to endpoint) were presented.

For subjects leaving the study prematurely, the last available data post-baseline were used for the final evaluation in accordance with the Last Observation Carried Forward (LOCF) method.

For the PP Population the LOCF were not applied, as the population had valid evaluations of the main parameters for all programmed visits.

For all efficacy parameters, the changes at the end of the study (week 13 or last post-baseline visit) compared to the baseline were used to characterise the treatment response in all subjects.

All tests were two-sided with a significance level fixed at the classical level of 5 %.

Statistical analysis and data listings were produced using the SAS version 8.2 package.

EFFICACY EVALUATION:

All subjects who received at least one dose of Paliperidone ER were included in the efficacy analysis (Intention-to-treat [ITT] Population).
For all efficacy parameters, the changes at the end of the study (week 13 or last post-baseline visit) compared to the baseline were used to characterize the treatment response in all subjects.
For efficacy evaluation the following scales were used:
PANSS (total score and subscale scores);
CGI-S;
PSP;
DAI 30
SWN 20;
an 11-point quality of sleep and daytime drowsiness evaluation scale;

SAFETY EVALUATION:

Adverse Events (AEs)
Subjects were instructed to report AEs as they emerged; AEs were assessed at each study visit after informed consent had been obtained.
Physical Examination
A physical examination was completed at baseline and at the end of the study (Week 13) or at early discontinuation. Any clinically significant abnormalities persisting at the end of the study were followed by the investigator until resolution or until reaching a clinically stable endpoint.
Pregnancy Test
A urine pregnancy test was completed in all females with childbearing potential at baseline, at week-13 (Day 91), or at early discontinuation.
Vital Signs
Vital signs included pulse and systolic and diastolic blood pressure.
Both measurements were done while the subject was sitting and after 5 minutes of rest. Vital signs were assessed at each scheduled visit of the 13-week treatment phase and at early discontinuation.
Body Weight
Subjects were weighed lightly clothed at baseline , at weeks 6 and 13, or at early discontinuation. The same amount of clothing had to be worn each time.
Extrapyramidal Symptom Rating Scale (ESRS)
Subjects were interviewed at study start (Visit 1), Week 2 (Visit 2), Week 6 (Visit 3), Week 13 (Visit 4) early discontinuation using the ESRS.
These scale was administered by a clinician, and had to be performed prior to treatment for EPS. If possible, the same person was to administer the scale at all visits.
Clinical Laboratory Tests
No clinical laboratory tests were performed.

EFFICACY CONCLUSION:

Paliperidone ER, administered at a variable dose (3-12 mg/day) in 132 schizophrenic patients with a disease duration <10 years showed to be very effective.
The administration, for a period of 3 months, in fact, originated a highly statistically significant reduction in the primary endpoint of the trial, that is the change in total PANSS score measured at the end of the study (Week 13 or last post-baseline evaluation).
This improvement occurred in both the PP and ITT populations.
The administration of Paliperidone ER was also accompanied by a statistically significant improvement in all the secondary endpoints considered:
Positive and Negative Syndrome Scale [PANSS] subscale scores for specific symptoms;
proportion of subjects improving ≥ 30% in total PANSS from baseline to endpoint
the subjective experience and attitude towards illness and medication (Subjective Well- being Under Neuroleptic [SWN 20] and Drug Attitude Inventory [DAI 30]
disease severity (Clinical Global Impression–Severity Scale [CGI-S]) personal and social functioning (Personal and Social Performance Scale [PSP])
quality of sleep and daytime drowsiness (11-point categorical evaluation scale)

These results are even more remarkable since all included patients were switched to Paliperdone ER from previous antipsychotics for efficacy and/or safety reasons.

SAFETY CONCLUSION:

Paliperidone ER proved to be safe and well tolerated.
The AEs recorded were sporadic, and no pattern or target organ/system could be observed.
Throughout the whole trial only one SAE occurred, while only 2/132 patients had to discontinue treatment for tolerability problems.

It is also worth noting that during the treatment with Paliperidone ER the ESRS showed a continuous improvement.

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