Janssen Research & Development

Synopsis
[Protocol INDIGOAPS1003; Phase 1]

INDIGO

Redaction and Removal of Information in This Document

- Information (including individual data listings, where applicable) has been removed or redacted to protect the privacy of patients, study subjects, and all named persons associated with the study. Names of companies other than Janssen Research & Development or Johnson & Johnson affiliates have been redacted, unless a contractual agreement is in place with those companies to disclose their names.
- Information has been removed or redacted to protect commercially confidential information.
- Aggregate data have been included, with any direct reference to an individual patient or study subject excluded.
- To disclose as much scientifically useful data as possible, no information other than that outlined above has been removed or redacted.

SYNOPSIS

Name of Sponsor/Company	Janssen Research & Development*
Name of Finished Product	To be determined
Name of Active Ingredient(s)	INDIGO

* Janssen Research & Development is a global organization that operates through different legal entities in various countries. Therefore, the legal entity acting as the sponsor for Janssen Research & Development studies may vary, such as, but not limited to Janssen Biotech, Inc.; Janssen Products, LP; Janssen Biologics, BV; Janssen-Cilag International NV; Janssen, Inc; Janssen Infectious Diseases BVBA; Janssen R&D Ireland; or Janssen Research & Development, LLC. The term "sponsor" is used to represent these various legal entities as identified on the Sponsor List.

Status: Approved

Date: 12 May 2015

Prepared by: Janssen Research & Development, LLC

Protocol No.: INDIGOAPS1003

Title of Study: Open-Label Pharmacokinetic Study to Evaluate the Steady-State Venous and Capillary Plasma Concentrations of 5 Antipsychotics: Aripiprazole, Olanzapine, Paliperidone, Quetiapine and Risperidone

EudraCT Number: 2013-005289-20

NCT No.: NCT02087579

Clinical Registry No.: CR103695

Coordinating Principal Investigator: [redacted] MD; [redacted] United States of America

Study Centers: 18 centers across 7 countries

Publication (Reference): None

Study Period: 28 February 2014 to 31 October 2014

Phase of Development: 1

Objectives: The primary objective of the study was to collect steady-state plasma concentration data for aripiprazole, olanzapine, quetiapine and their relevant metabolites to generate dose- and time-related population reference ranges for these antipsychotics.

The data generated in this study were also used to compare fingerstick-based capillary plasma vs. venous plasma concentrations of aripiprazole, olanzapine, paliperidone, quetiapine, risperidone and their relevant metabolites.

In addition, safety was evaluated.

Methodology: This was an open-label, parallel-group, multiple-dose, multicenter study in psychiatric subjects who were receiving stable doses of aripiprazole, olanzapine, paliperidone, quetiapine and/or risperidone for the treatment of their disease. This study included a screening phase (within 21 days before Day 1) followed by a 3-day observation phase (Day 1 to Day 3 at the study center) and early withdrawal assessments or end-of-study assessments on Day 3. Subjects were allowed to return for up to a week after the end-of-study assessments to address any medical or psychiatric concerns. During the

3-day observation phase, the administration of the prior antipsychotic medication (study drug) continued at a subject's usual dose and dosing schedule under direct observation of the study staff. The total study length was 3 days, excluding the screening phase.

The following cohorts were included in the study:

- Cohort A: Aripiprazole oral formulation
- Cohort B: Olanzapine oral formulation
- Cohort C: Paliperidone prolonged-release (extended-release) tablets or paliperidone long acting injectable (LAI; ie, paliperidone palmitate) injections
- Cohort D: Quetiapine oral formulation
- Cohort E: Risperidone oral formulation or risperidone LAI injections

A venous blood sample was collected for PK sampling from all subjects at 8 scheduled sampling timepoints. For a subset of 20 subjects in each cohort, fingerstick-based capillary blood samples were collected at 6 of the 8 scheduled sampling timepoints immediately after the venous sample. Safety was evaluated throughout the study and a mandatory pharmacogenomic blood sample was collected for analysis of genes that may influence exposure of the antipsychotics studied.

Number of Subjects (planned and analyzed):

Planned: A total of 265 subjects were planned to be enrolled in the study.

Analyzed: A total of 305 subjects were enrolled and received the study drug. All the subjects were included in the safety analysis.

Diagnosis and Main Criteria for Inclusion: Healthy men or women between 18 and 70 years of age (inclusive), body mass index (BMI) between 17 and 40 kg/m^2 (inclusive), and body weight not less than 47 kg, receiving treatment with aripiprazole, olanzapine, paliperidone, quetiapine or risperidone or a combination of these antipsychotics as therapy for the treatment of their disease were eligible to participate in the study.

Test Product, Dose and Mode of Administration, Batch No.: The subjects took their own medication as prescribed by their regular clinician; ie, the same brand name or specific generic manufacturer and the same oral formulation of the same antipsychotic drug on which they were stable before the study.

Reference Therapy, Dose and Mode of Administration, Batch No.: Not Applicable

Duration of Treatment: The duration of the observation phase was 3 days, during which administration of the prior antipsychotic medication continued at a subject's usual dose and dosing schedule under direct supervision of the study staff.

Criteria for Evaluation:

Drug Concentration Measurements:

On Days 1 to 3, the following samples were collected for determination of plasma drug concentrations of the antipsychotic drugs:

- all subjects: a venous blood sample (3 mL),
- subgroups fingerstick + venous: a fingerstick capillary blood sample (0.5 mL).

For subjects taking aripiprazole, both the concentrations of aripiprazole and dehydroaripiprazole metabolite were determined. For subjects taking quetiapine, the concentrations of quetiapine and quetiapine metabolites (quetiapine sulfoxide, norquetiapine and 7-hydroxyquetiapine) were determined.

For subjects taking risperidone, both the concentrations of risperidone and the 9-hydroxyrisperidone (paliperidone) metabolite were determined.

Pharmacokinetics:

Analyses were performed using population-pharmacokinetic (POP-PK) modeling. No pharmacokinetic (PK) parameters were calculated using non-compartmental approaches.

All the concentration data of aripiprazole, olanzapine and quetiapine and their measured metabolites were subjected to a formal POP-PK analysis using nonlinear mixed effects modeling (NONMEM) approaches.

The results of the population PK analyses are reported separately.

Pharmacogenomic Analyses:

A composite genotype and predicted phenotype were derived from the raw genotyping data. The genotyping only involved genes thoughts to be involved in the metabolism of the selected antipsychotic medication. The details will be provided in the population PK report.

Safety Analyses:

Safety was evaluated by examining the incidence and type of adverse events, and changes in vital signs, Columbia Suicide Severity Rating Scale (C-SSRS), and physical examination results, from the screening phase through study completion.

Statistical Methods:

Sample size determination: A total of 75 subjects per cohort were planned to be enrolled, as this number was considered adequate to build a robust POP-PK model. For the comparison of capillary vs. venous drug concentrations, initially 20 subjects were planned to be selected per cohort. Based on an exploratory analysis of approximately 12 subjects per cohort, it was decided to select more subjects on Quetiapine and Olanzapine for this evaluation.

Pharmacokinetic analysis: Primary analyses were performed by using POP-PK modeling to derive dose-related population reference ranges for aripiprazole, olanzapine, and quetiapine. The results of the population PK analyses are reported separately.

Drug Concentration Measurements: For each cohort and dose, individual data were listed for all subjects and descriptive statistics were calculated at each sampling time for fingerstick-based capillary plasma concentrations and venous plasma concentrations, for all analytes and for the calculated sums of parent drug and metabolite separately. Descriptive statistics included arithmetic mean, standard deviation, coefficient of variation, median, minimum, and maximum.

For each antipsychotic drug, Deming regression models were fit to the individual log transformed capillary concentrations with corresponding individual log transformed venous concentration as a predictor to evaluate the relationship. Concordance correlation coefficients between the 2 sample types were calculated for each cohort.

The individual percentage difference between fingerstick-based capillary vs. venous plasma concentrations was calculated at each timepoint for each analyte and for the calculated sums of parent drug and metabolite(s), and descriptive statistics were calculated.

Visual presentations of the comparison of capillary vs. venous drug and metabolite concentrations include Bland-Altman plots, box- and whiskers plots and scatter plots.

Safety analysis: All subjects for whom at least one sample (fingerstick capillary or venous sample, including if it was only a partial sample) was taken for drug concentration measurement were included in the safety analysis.

Adverse events were tabulated by system organ class. Individual events (preferred term) within each system organ class were presented in order of descending frequency. They were also tabulated by severity and relationship to study-related procedures and were presented by cohort.

Summaries, listings, datasets, or subject narratives were provided, as appropriate, for those subjects who died, who discontinued treatment due to an adverse event, or who experienced a severe or a serious adverse event.

Descriptive statistics of temperature, pulse/heart rate, and blood pressure (systolic and diastolic) (supine and standing) values and changes from baseline were summarized at each scheduled timepoint by cohort. The percentage of subjects with values beyond prespecified clinically important limits was summarized. Results of physical examinations and laboratory tests were listed. The ECG variables heart rate, RR interval, PR interval, QRS interval, QT interval and QTc using QTcB and QTcF were listed. For the C-SSRS, suicide-related thoughts and behaviors were summarized by cohort over time with incidence and shift tables.

RESULTS:

STUDY POPULATION: A total of 305 subjects (aripiprazole=83, olanzapine=95, paliperidone=24, quetiapine=82, and risperidone=21) were included in the safety set. Of the 305 subjects, 304 (99.7%) subjects completed the study. One subject was withdrawn from the study due to an adverse event (AE) of increased blood pressure.

The subjects had a median age of 46.0 years (range: 18-67 years), a mean (SD) baseline weight of 87.1 (17.50) kg, and a mean (SD) baseline BMI of 29.7 (5.20) kg/m^2. There were more men (n=198 [64.9%]) than women (n=107 [35.1%]), and the majority (n=184 [60.3%]) of the subjects were White. Protocol deviations were reported in 16 subjects in this study.

PHARMACOKINETIC RESULTS:

A total of 2462 paired concentration records from 181 subjects were included in the statistical comparison of capillary and venous concentrations.

Based on the regression analyses a linear correlation between capillary and venous plasma concentrations was observed for all measured parent drugs, metabolites and sums of parent drug and metabolite. Except for olanzapine, no statistically significant differences were found between the capillary and venous concentrations: the intercepts of the regression lines were not significantly different from 0 and the slopes were not significantly different from 1 for the parent drugs, the measured metabolites and the sums of parent drug and metabolite.

Median percentage differences were below 10% for most, and below 22% for all compounds and timepoints. No clear relationships were observed between the percentage differences and the time after dosing or the drug formulation, though a trend for lower percentage differences was observed for drugs with less fluctuation, ie, for the extended-release (ER) and LAI formulations and for aripiprazole, a drug with a long half-life.

Individual cases of high percentage differences were observed and evaluated. These were only present for subjects taking immediate release (IR) formulations, at low venous concentrations, and in all these cases the capillary concentration was greater than the venous concentration. The median differences observed are considered clinically irrelevant given the typical intra- and inter-subject variability in drug plasma concentrations and given that the (mean) absolute difference in capillary versus venous concentrations is relatively low.

SAFETY RESULTS: A total of 22 (7.2%) subjects reported at least 1 treatment emergent adverse event (TEAE) during the study. Overall, 3 (3.6%) subjects in Cohort A, 8 (8.4%) subjects in Cohort B, 3 (12.3%) in Cohort C, 7 (8.5%) in Cohort D, and 1 (4.8%) subject in Cohort E reported TEAEs.

The system organ classes (SOCs) with a higher incidence of TEAEs were gastrointestinal disorders, nervous system disorders, and psychiatric disorders. The most commonly reported TEAEs (≥2) were headache (6 [2.0%] subjects), anxiety (3 [1.0%] subjects), dyspepsia, toothache, and insomnia (2 [0.7%] subjects each).

Most of the TEAEs were considered by the investigator to be mild in intensity. There were no TEAEs that were severe in intensity. All the TEAEs were considered by the investigator to be not related to the study drug, except for an event of dry mouth that was considered to be probably related to the study drug. There were two vessel puncture site reactions related adverse events (Vessel puncture site haematoma and Vessel puncture site pain) which were considered as related to the study procedures.

No deaths were reported in this study. Two subjects were reported with serious adverse events (SAEs) of which, one was a screen failure who was reported with SAEs of psychiatric disorder and convulsions and another was reported with an event of psychotic disorder 2 days after the completion of the study. One subject was withdrawn from the study due to an AE of increased blood pressure.

There were no unexpected safety findings in this study, including changes in the clinical laboratory analytes and vital signs parameters or physical examination. None of the ECG abnormalities were considered as clinically relevant and none were reported as TEAEs.

STUDY LIMITATIONS

No notable study limitations were identified by the Sponsor

CONCLUSIONS:

A linear correlation between capillary and venous plasma concentrations was observed for all measured parent drugs, metabolites and sums of parent drug and metabolite. For olanzapine, capillary concentrations were slightly higher than venous concentrations. The data support that, after repeated dosing, systemic drug concentrations using fingerstick sampling reflect drug concentrations using venous sampling. Therefore capillary sampling may be appropriate as alternative to venous sampling to evaluate systemic drug concentrations and assess treatment adherence. Population-PK models and reference ranges derived from them will be reported separately.

The study procedures were generally well tolerated and no new or unusual safety signals were noted during the conduct of this study. The capillary sampling was well tolerated.

Disclaimer

Information in this posting shall not be considered to be a claim for any marketed product. Some information in this posting may differ from, or not be included in, the approved labeling for the product. Please refer to the full prescribing information for indications and proper use of the product.