2 STUDY SYNOPSIS

Name of Company: Janssen Research & Development	INDIVIDUAL STUDY TABLE	(For National Authority Use Only)
Name of Finished Product: AcipHex®	Referring to Part IV of the Dossier **Volume:** **Page:**	
Name of Active Ingredient: Rabeprazole Sodium		

Study Title

A Pharmacokinetic, Pharmacodynamic, and Safety Study of Single- and Multiple Doses of Rabeprazole in Pediatric Subjects with GERD 1 to 11 Months old, Inclusive

Investigator(s)/ Site(s)

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Publication (Reference)

None

Study Period

Total study period was from 14 April 2008 to 29 February 2012 (1,416 days)

Phase of Development

Phase 1

Objective(s)

The objectives of this study were to evaluate the pharmacokinetics (PK), pharmacodynamics (PD), (intraesophageal/intragastric pH, clinical global impressions [CGI], formulation palatability, and gastro esophageal reflux disease [GERD] daily symptom diary), and safety of rabeprazole after single and multiple daily administration at 2-dose levels in children between the ages of 1 and 11 months, inclusive (up to 11 months 29 days), with GERD.

Methodology

This was planned as an open-label, multicenter study consisting of 2 parts. Part 1 of RABGRD1003 was a preliminary dose finding study to gather PK and safety data to inform the choice of a dose for Part 2 and for a later planned Phase 3 study of rabeprazole in 1-11 month old infants with GERD (RABGRD3004).

Part 1: (at least 9 subjects) was non-randomized, with 2 subjects receiving 0.14 mg/kg rabeprazole and the remaining 10 subjects receiving 0.5 mg/kg rabeprazole in 1 mg increments.

In **Part 2** (at least 24 subjects), subjects were planned to be randomized into 1 of the 2 dose groups (5- and 10-mg rabeprazole) with at least 12 subjects randomized to each dose group.

Each part consisted of 3 phases: a pretreatment phase (screening period starting up to 21 days before treatment), a treatment phase, and a posttreatment phase lasting at least 2 weeks after the final drug administration or the time of early withdrawal.

During the treatment phase, there were 2 options (both for Part 1 and Part 2 of the study).

Option 1: Once daily doses of rabeprazole each morning for 5 days with serial PK sampling (7 samples per day) on Day 1 and Day 5.

Option 2: Once daily doses of rabeprazole each morning for up to 14 days (10 days minimum) with sparse PK sampling (2 samples per day) on Days 1, 5, and 10. Subjects with a weight of less than 5 kg were mandated to be treated according to Option 2.

Single-dose PK and PD evaluations were done post dosing on Day 1. Multiple-dose PK and PD evaluations were

done at the presumed steady-state after the fifth dose on Day 5 (Option 1), or after the fifth and tenth dose on Day 5 and Day 10 (Option 2). Clinical global impression, formulation palatability, and GERD daily symptom diary evaluations were done at the presumed steady-state on Day 5 for subjects in Option 1, and on Day 5 and Day 10 for subjects in Option 2.

In Part 1 of the study, the first 2 subjects enrolled received 0.14 mg/kg, which mimicked the mg/kg dose received by a 70 kg adult taking 10 mg rabeprazole; a dose known to result in a target drug exposure (AUC) in adults of 400 ng.h/L. When this dose in infants resulted in AUCs well under the target range, the dose was increased to 0.5 mg/kg for all the remaining subjects in Part 1, using increments of 1 mg. Enrollment for Part 2 was started after the assessment of safety/tolerability and PK data in Part 1 of the study.

Number of Subjects (Planned and Enrolled)

Planned: Approximately 33 subjects; at least 9 subjects in Part 1 and at least 24 subjects in Part 2 (randomly assigned to 2 dose groups of at least 12 subjects each) were planned to enter into the open-label treatment period.

Enrolled: A total of 70 subjects were screened and 50 subjects were enrolled in the study. Of these 50 subjects, 12 subjects were enrolled in Part 1 (2 subjects in the 0.14-mg/kg dose group and 10 subjects in the 0.5-mg/kg dose group), and 38 subjects were enrolled in Part 2 (19 subjects each randomized to the 5-mg and 10-mg dose groups respectively). Six subjects in each dose group of Part 2 who required intraesophageal pH monitoring for clinical management, were planned to have dual-channel combined intraesophageal/intragastric pH probe assessments.

Diagnosis and Main Criteria for Inclusion

Boys and girls, 1- to 11-months-old inclusive (with parent[s] or legally-acceptable representative [LAR] signing consent for participation), weighing a minimum of 5 kg (Option 1) or 3 kg (Option 2) who had a diagnosis of suspected GERD, based on the presence of recurrent vomiting or regurgitation, were enrolled in the study.

Test Treatment, Dose, Mode of Administration, and Batch Number(s)

In both Part 1 and Part 2, rabeprazole enteric-coated granules were orally administered, once daily in the morning at the same time (±30 minutes) after a period of overnight fasting. Food was to be withheld until 30 minutes after dosing. Thirty minutes after dosing subjects were allowed to consume a light meal and then allowed to resume a normal diet 1 hour after dosing.

Part 1: Rabeprazole granules (orange-colored) were supplied in sachets containing either 1-mg or 5-mg rabeprazole. A drug-vehicle suspension was prepared by combining separate sachets of the rabeprazole granules and inactive vehicle granules and then reconstituting with water while mixing. Inactive strawberry-flavored vehicle granules (pink-colored) were supplied in 0.2-g or 1-g dose sachets. The amount of rabeprazole dose (0.14 mg/kg for the first 2 subjects and 0.5 mg/kg for the next 10 subjects) was adjusted according to the subject's weight.

Part 2: Rabeprazole granules (white to off-white colored) were supplied in a white sprinkle capsule containing 5 mg of rabeprazole. Rabeprazole granules – at a dose of 5 or 10 mg - were sprinkled on a small amount of soft food (yogurt or any type of pureed fruit) or mixed with formula or expressed breast milk. If the amount of sprinkles was too large for a single spoonful of soft food, it was given with several spoonfuls of food. Alternatively, the dose was administered in formula by placing the rabeprazole granules in a syringe containing approximately 5 mL of formula and slowly administering the contents of the syringe over a short period of time. For infants who were solely breastfed, the rabeprazole granules were mixed with expressed breast milk immediately before dosing and administered in the same way as if mixed in formula.

The PK results from Part 1 of the study were assessed to determine the 2 dosages to be studied in Part 2.

Batch Number: The entire list is presented in Section 9.4.2 Identity of Investigational Product(s).

Duration of Treatment

In Part 1, subjects were treated with open-label rabeprazole for approximately 5 days (Option 1) or 10 to 14 days (Option 2), and enrolled for a maximum of 7 weeks. In Part 2, subjects were planned to be treated with open-label rabeprazole for 5 to 28 days (Option 1 and Option 2), and enrolled for a maximum of 9 weeks.

Assessments

PHARMACOKINETIC EVALUATIONS

Venous or capillary blood samples (0.4 mL each) for determination of rabeprazole and thioether metabolite plasma concentrations were collected at predose, and at 1, 2, 4, 6, 8, and 12 hours postdose on Day 1 and Day 5 (Option 1; semi-rich PK sampling), or at approximately 2, and 4 hours postdose on Day 1 and Day 5, and at approximately 5 and 6 hours postdose on Day 10 (Option 2; sparse PK sampling).

Plasma concentration data of rabeprazole and the thioether metabolite of rabeprazole collected in Part 1 and Part 2 of the study were listed.

For Option 1, PK parameters were estimated for rabeprazole and its thioether metabolite using non compartmental analysis. In addition, all data collected from Option 1 and Option 2 will be combined with PK data from other pediatric and adult studies and subjected to a population PK analysis approach to assess the PK or rabeprazole in this age group and to estimate key PK parameters for rabeprazole. Details about the population PK analysis and its results will be reported in a separate report.

PHARMACODYNAMIC EVALUATIONS

Pharmacodynamic intraesophageal/intragastric pH assessments were performed in at least 12 subjects in Part 2 (at least 6 subjects per dose group) who required intraesophageal pH monitoring for clinical management. Intraesophageal/Intragastric pH was assessed by measuring the following baseline (Day -1) and dose interval (Day 1 and Day 5) PD parameters: Intraesophageal and Intragastric AUC of the hydrogen ion concentration over time, the percentage of time with intragastric pH >3 and >4; the percentage of time that intraesophageal and intragastric pH was <4; and the number of intraesophageal reflux events and number of prolonged (>5 minutes) intraesophageal reflux events.

Clinical Global Impression of severity of illness subscale (CGI-S) was assessed on Day -1 and Global Change subscale (CGI-C) on Day 5 (Option 1), or on Day 5 and Day 10 (Option 2). In Part 2, for subjects in Option 1, CGI-S and CGI-C was assessed on Day 10 for those subjects who were eligible to continue dosing beyond Day 5.

Global Assessment of Effectiveness (GAE): The effectiveness of treatment was rated on Day 5 (Option 1), or on Day 5 and Day 10 (Option 2). In Part 2, for subjects in Option 1, GAE was also assessed on Day 10 for those subjects who were eligible to continue dosing beyond Day 5.

Palatability (including ease of swallowing) of the study drug was assessed daily by the subject's parent(s) or LAR as indicated in the Time and Events Schedule.

PHARMACOGENOMIC EVALUATIONS

Buccal swab samples (pharmacogenomic samples) were collected on Day 1 from subjects whose parent(s) or LAR provided consent to the pharmacogenomic component of the study to allow for CYP2C19 analysis. Subject participation in the pharmacogenomic research was optional.

SAFETY EVALUATIONS

Safety was assessed through monitoring of concomitant therapies and adverse events (AEs) throughout the study; and clinical laboratory testing at baseline and post treatment including hematology, clinical chemistry, and urinalysis assessment. Vital signs, 12-lead electrocardiogram, and physical examination including body weight and length were also performed before and after treatment.

Bioanalytical Methods

Plasma concentrations of rabeprazole and its thioether metabolite were determined using a validated, specific, and sensitive liquid chromatographic/mass spectrometry assay under the supervision of the sponsor's bioanalytical facility.

Statistical Methods

SAMPLE SIZE DETERMINATION

The sample size for this study was expected to provide sufficient data by treatment Option 1, treatment Option 2, or a combination of data from each treatment option to allow for a reasonable assessment of the PK of rabeprazole in children 1 to 11 months of age, inclusive.

PHARMACOKINETIC ANALYSES

Plasma concentrations of rabeprazole and its thioether metabolite were listed and summarized using descriptive statistics by dose group and treatment day (for both Option 1 and Option 2 separately). In addition for the PK samples collected in Option 1 (semi-rich sampling), PK parameters, estimated via non compartmental analysis, were listed by dose group and treatment day.

Additionally, plasma concentration data collected from Option 1 and Option 2 were included, along with data from other pediatric studies, in a population PK analysis (to be reported separately) to estimate key PK parameters for rabeprazole.

PHARMACODYNAMIC ANALYSES

Intraesophageal/intragastric pH parameters were listed and summarized using descriptive statistics for the baseline assessment and by dose group and treatment day. Results from the CGI-S, CGI-C, GAE, and palatability assessment along with GERD daily symptom diary were listed and summarized using descriptive statistics by dose group.

PHARMACOGENOMIC ANALYSES

Allele and genotype frequencies for analyzed genes were tabulated. Selected PK and efficacy endpoints were to be explored for association with analyzed genes.

SAFETY ANALYSES

Safety analysis was performed on all subjects who received at least one dose of the study drug.

Safety was evaluated by examining the incidence and type of AEs and changes in clinical laboratory test values, physical examination results and vital signs measurements from baseline through to the end of the study/early withdrawal. Safety data was summarized by individual treatment group, as well as the combined active treatment group.

Based on the safety/tolerability results obtained from Part 1 of the study, enrollment for Part 2 was to begin after it was agreed by the Janssen Research & Development, L.L.C. study physicians and medical monitors, and the investigators (from the site) that the study drug was safe and well-tolerated by the subjects in Part 1. In both Parts 1 and 2, a Data Safety Monitoring Board (DSMB) reviewed the data after approximately 25%, 50%, and 75% of subjects completed the study and recommended further continuation of study without alteration of the study protocol after each of these reviews.

Results

After the completion of Part 2, including the last patient out and database lock events, it was discovered that approximately 50% of the total analyzed blood samples from all subjects had no measurable drug concentrations. An investigation into this finding revealed that a batch of placebo capsules was mislabeled as active 5-mg rabeprazole capsules at the main clinical supply storage, labeling, and shipping facility. This batch was then shipped to 7 sites participating in this study. As a result, 19 of the 38 subjects enrolled in Part 2 were either completely (18 subjects) or partially exposed (1 subject) to mislabeled placebo. The 1 partially exposed subject received partial placebo plus partial rabeprazole 5 mg. A 20^{th} subject was treated either completely with placebo or may have received a combination of rabeprazole (on Day 1 of dosing), and placebo on the remaining days of dosing.

Subject Disposition/Analysis Sets

Seventy subjects were screened for the study and 20 of these subjects were screening failures. Two subjects enrolled in Part 1 were administered rabeprazole 0.14 mg/kg and 10 subjects received rabeprazole 0.5 mg/kg. All 12 subjects completed Part 1.

Thirty-eight subjects were randomized in Part 2, including 9 subjects who received rabeprazole 5 mg; 9 subjects who received rabeprazole 10 mg; 18 subjects who received placebo; and 1 subject who received a combination of placebo [for the first 9 days] and rabeprazole 5 mg [for the last 8 days]). An additional subject was excluded from the analysis of data due to uncertainty about whether that subject had been exposed to active drug on the first day of dosing or treatment and subsequently exposed to only placebo on all other days of dosing

The following data sets were analyzed in this study:
Safety Analysis Set: All subjects who were randomized and received at least 1 dose of study drug.
Pharmacodynamic Analysis Set: All subjects who were randomized, received study drug, and had at least one PD

measurement.
pH Analysis Set: All subjects who were randomized, received study drug, and had pH measurements for at least one day.
All Subjects Analysis Set: All subjects including the safety analysis set and screen failures.

Pharmacokinetics, Pharmacodynamics Pharmacogenomics/Pharmacogenetics

- Plasma concentrations measured on Day 1 and Day 5 were in the same order of magnitude; the PK data did not indicate drug accumulation over the 5 day dosing period. Plasma concentrations of rabeprazole and its thioether metabolite showed considerable inter-subject variability.
- Overall exposure to study drug was equivalent in the placebo exposed-group vs. the rabeprazole-exposed groups implying that investigator judged improvement that allowed continued dosing from Day 5 to Day 10, or from Day 10 to a maximum of 28 days, was equally distributed between subjects on rabeprazole and those on placebo.
- The paucity of subjects who were both exposed to rabeprazole and collected semi-rich PK blood samples precluded deriving meaningful PK parameters (AUC, C_{max}) from these limited data alone.
- Across the variability observed in the small sample of subjects with semi-rich data on 5 mg (N=2) and 10 mg (N=2), AUC values were either within or approximated the 400 to 800 ng.h/mL AUC-bracket that is associated with clinical efficacy in the 10- to 20-mg adult dose range.
- Pharmacodynamic conclusions derived from prolonged pHmetry studies are hampered by the limitation of having only one subject who received rabeprazole (10 mg qd) and underwent all 3 pH studies. However, suppression of intragastric acid and reductions in intraesophageal reflux and prolonged reflux events were evident in this subject by Day 5 of dosing with rabeprazole, whereas the same changes were not seen in subjects who were exposed to placebo only.
- Changes in CGI-C and GAE, and in the GERD symptom diary subscores appeared to be similar in each of the rabeprazole dose groups vs. the placebo group. Improvements were seen over the course of the study in many subjects exposed to both active drug and placebo for the short duration of the study.

Safety

- No new safety signals were identified in this study.
- Equal numbers of treatment- emergent adverse events (TEAEs) and treatment-emergent serious adverse events (TESAEs) were reported in subjects exposed to rabeprazole vs. placebo; and no increase in TEAEs or TESAEs was seen in subjects administered 10-mg qd rabeprazole compared with subjects receiving 5 mg qd or 0.5 mg qd.
- The most common AEs (>5% of total subjects) were nasopharyngitis, vomiting, and diarrhea; 1 subject with vomiting and 1 subject with diarrhea were receiving placebo.
- Most AEs were not judged to be related to study drug with the exception of 3 subjects (6.1%) with possibly related AEs including vomiting (rabeprazole 10 mg), diarrhea (rabeprazole 0.5 mg/kg), and nosocomial infection (placebo).
- There were no laboratory, vital sign, or electrocardiogram (ECG)-related safety signals noted. The mean increase in end of study (EOS) serum gastrin in rabeprazole-treated subjects versus those who received placebo that was more pronounced in the 10-mg versus the 5 mg rabeprazole group, and was expected based on the known pharmacology of rabeprazole.

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