2 STUDY SYNOPSIS

Name of Company: Janssen Research & Development, LLC	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		

Title of Study:	A Pharmacokinetic, Pharmacodynamic and Short-term Safety Study of Single and Multiple Day Doses of Rabeprazole Sodium in Neonates and Pre-term Infants with a Corrected Age of Less than 44 Weeks with a Presumptive Diagnosis of GERD
Investigator(s) Center(s):	22 Principal Investigators participated in the study; 69 randomized subjects Multicenter (22 sites) including 14 in United States, 4 in Poland, 3 in United Kingdom and 1 in Germany
Publication (Reference):	None
Study Period and Phase of Development:	This Phase 1 study was initiated on 21 February 2010 and was completed on 14 January 2012. The total study duration from First Patient In (FPI) to Last Patient Out (LPO) was 99 weeks (692 days).
Objective(s):	The objectives of the study were to evaluate the pharmacokinetics (PK) using population PK methods, pharmacodynamic (PD) (intraesophageal and intragastric pH, assessment of the overall treatment effect [OTE] [overall Gastroesophageal Reflux Disease (GERD) symptom relief]), and the short-term safety of rabeprazole after single- (Day 1) and multiple (Day 5) once daily dose administration for up to 28 days at 1 low dose level (Part 1) and 2 presumed effective dose levels (Part 2) in neonates and pre-term infants, with a corrected age of less than 44 weeks at the time of the first dose, who had been diagnosed with GERD.
Methodology:	This was an open-label, multi-center, Phase 1 study in neonates and pre-term infants who received once daily doses of rabeprazole for at least 5 days. This study consisted of 2 parts, Part 1 and Part 2. Each part of the study consisted of 3 phases: • Pre-treatment phase (screening of up to 7 days): Informed consent obtained and subjects were assessed for eligibility to participate • The open-label treatment phase (up to 4 weeks): In Part 1, subjects received a dose of 1-mg rabeprazole sodium every 24 hours for at least 5 days and a maximum of 28 days. In Part 2, subjects were randomly assigned to 2 dose groups to receive either 2-mg or 3-mg rabeprazole sodium once daily for at least 5 days and a maximum of 28 days.

	• Posttreatment phase (14 to 21 days after the last dose of study drug): A safety evaluation 14 to 21 days after the last dose administration was performed for all subjects who completed or who prematurely discontinued participation in the study. The maximum study duration (including the screening period) was approximately 8 weeks.
Number of Subjects (planned and analyzed):	At least 60 subjects (minimum 14 subjects in Part 1 and minimum 46 subjects with 23 subjects in each of 2 dose groups in Part 2) were planned to be enrolled in this study. Subjects who discontinued before the fifth dose (in both Part 1 and Part 2) were replaced. Sixty-nine subjects were analyzed in this report; 19 in Part 1 and 50 in Part 2 (25 in each of two dose groups: 2 mg and 3 mg).
Diagnosis and Main Criteria for Inclusion:	Male or female neonates or pre-term infants with a corrected age of less than 44 weeks, with a minimum weight of 0.8 kg at screening, with a presumptive diagnosis of GERD, who were inpatients in a neonatal intensive care unit (NICU) or step-down unit, and who required a feeding-tube (≥6 French [F] nasogastric [NG] or orogastric [OG]) for partial or full enteral alimentation.
Test Product, Dose, Mode of Administration, and Batch No(s):	**Test Treatment, Dose, Mode of Administration, and Batch Number:** In both Part 1 and Part 2, rabeprazole enteric-coated (EC) granules were administered through NG or OG tube. Feeding was to be avoided 15 minutes before and after dosing. **Part 1:** Rabeprazole granules (orange colored) supplied in 1-mg dose sachets. **Part 2**: Rabeprazole granules (white clear) were provided as 1 mg sprinkle capsules (white to off-white). **Mode of administration**: The study drug was administered through a ≥6 F NG or OG tube as a suspension of rabeprazole granules, inactive vehicle granules (or vehicle tablet under Protocol Amendment 2) and water. Strawberry-flavored inactive vehicle granules were provided in 0.2 g sachets. Under Protocol Amendment 2, the drug-vehicle suspension was prepared using a vehicle tablet. The lot/batch number and expiry date of study drug are provided below: **Part 1 (rabeprazole)**: Packaging lot no. = P8 5003AAA; Granule lot no. = P85003AA; Expiry date = April 2011. **Part 2 (rabe prazole)**: Packaging lot no. = P92 013AAB; Granule lot no. = P92013AA; Expiry date = January 2012.
Duration of Treatment:	Subjects received once daily doses of rabeprazole sodium (1 mg for Part 1 and either 2 mg or 3 mg for Part 2) for at least 5 days and a maximum of 28 days.
Criteria for Evaluation:	**Pharmacokinetics** Two blood samples (0.4 mL each) for determination of the plasma concentration of rabeprazole and its thioether metabolite were collected on Day 1 (after single-dose) and Day 5 (after multiple once daily dosing; at presumed steady-state) for both Part 1 and Part 2. On each of these days, one PK sample was obtained between 2-hours and 3-hours post dose and another between 3-hours and 4-hours postdose,

	with at least 1-hour interval between the two PK sample collections. **Pharmacodynamic** A 24-hour dual channel intraesophageal and intragastric pH assessment was done for all subjects in Part 1 and at least 12 subjects in Part 2 (at least 6 subjects from each dose group). The intragastric pH assessments were conducted at baseline (Day -1; prior to the first dose of rabeprazole), after a single dose (Day 1), and after 5 daily doses (multiple dose on Day 5). The assessments on Day 1 and Day 5 started within 1 hour of dosing with rabeprazole. Each pH assessment continued for 22 to 24 hours. Pharmacodynamic variables were as follows: intraesophageal and intragastric AUC of the H+ concentration over time, percentage of time with an intraesophageal and intragastric pH of ≥3, percentage of time that the intraesophageal and intragastric pH of ≥4, percentage of time that the intraesophageal and intragastric pH of <4, mean intragastric pH, number of reflux events, and prolonged reflux events (each lasting >5 minutes). Comparisons were made between the 3 days of pH measurement (Day -1 baseline, Day 1 of dosing, and Day 5 of dosing) within each dose group (day effect); and between the 3 dose groups (1 mg, 2 mg, and 3 mg) within each day of measurement (dose effect). The investigator performed an OTE by assessing the overall GERD symptom relief (Better, No change, or Worse) on Day 5, Day 10, and Day 28 of treatment relative to baseline (Day -1). **Safety** Safety and tolerability was assessed throughout the study by monitoring adverse events (AEs), hematology and serum chemistry, urinalysis, physical examination including weight and length, and vital sign measurements.
Bioanalytical Methods:	The plasma concentrations of rabeprazole sodium and its thioether metabolite were determined using a validated, specific, and sensitive high-performance liquid chromatographic-mass spectrometry/mass spectrometry assay (LC-MS/MS) under the supervision of the sponsor's bioanalytical facility.
Statistical Methods:	SAMPLE SIZE DETERMINATION The sample size was not based on statistical considerations. At least 60 subjects were planned to be enrolled in the study. This sample size was considered sufficient to achieve the study objectives. PHARMACOKINETICS: Plasma concentrations of rabeprazole and its major thioether metabolite were summarized and graphically displayed. Because only sparse PK sampling was done for all subjects, no quantitative PK parameters (AUC, C_{max}, etc) were calculated. Pharmacokinetic data obtained in Part 1 and Part 2 of the current study was included in a population PK analysis to estimate the key PK variables of rabeprazole. Details and results of the population PK analysis (which also included PK data from older children and adults) to characterize the PK of rabeprazole in this age group is contained in a separate report. PHARMACODYNAMICS: Intraesophageal and intragastric pH variables were listed and summarized with

	descriptive statistics for the baseline (Day -1) assessment and by dose group (1, 2, and 3 mg) and treatment day (single-dose Day 1 and multiple once daily dosing on Day 5). The PD study drug effect was assessed by change from baseline in the PD variables and listed and summarized by descriptive statistics and graphical displays. The OTE (overall GERD symptom relief) on specific timepoints relative to baseline (Day -1) was listed and summarized by dose group. SAFETY: All subjects who were enrolled and received at least 1 dose of study drug were included in the safety and tolerability analysis. Safety was evaluated by assessment of 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 were summarized by individual treatment group, as well as the combined active treatment group. Descriptive statistics were provided to evaluate the changes in the safety parameters at each scheduled timepoint.
Results:	**Pharmacokinetics:** Plasma concentrations measured at Day 1 and Day 5 were in the same order of magnitude; and thus the sparse PK data did not indicate drug accumulation over the 5 day dosing period. Plasma concentrations of rabeprazole and its thioether metabolite were highly variable and a dose (both absolute and body-weight corrected)-dependent increase change in plasma concentrations of rabeprazole and thioether metabolite was not apparent. Based on graphical exploration of the sparse PK information, neither body weight nor age appeared to have a clear effect on the plasma exposure of rabeprazole or its thioether metabolite. **Pharmacodynamics:** • Because of skewness and high variability of data, non-parametric analysis (Wilcoxon signed rank tests) was used for the AUC of the hydrogen ion concentration. Exposure to all three doses (1 mg, 2 mg, and 3 mg) resulted in significant suppression of the AUC of the intragastric [H+] on Day 1 of dosing and Day 5 of dosing compared to baseline (Day-1). The median percent change for intragastric AUC for Day 1 (Day 1 as percentage of Day 5) for 1 mg, 2 mg and 3 mg were 99.99%, 97.93% and, 99.65% respectively, indicating that the major portion of acid suppression was already present on the first day of dosing. • This result was supported by the demonstration (by analysis of variance and pairwise comparisons) of statistically significant decreases in the % time intragastric pH<4.0 and <3.0 and increases in the % time intragastric pH>4.0 and >3.0 in all 3 dose groups on both Day 1 and Day 5 of dosing compared to baseline. Mean intragastric pH rose significantly from Day-1 through Day 5 in all three dose groups. Although there was a significant day effect in all 3 dose groups, there was no statistically significant dose effect in any of the above mentioned parameters. Thus, there was no evidence that higher doses (2 mg or 3 mg) suppressed intragastric acid more significantly than the 1-mg dose in this population. • Non parametric analysis of the intraesophageal [H+] showed a statistically

	significant decrease between Day -1 baseline vs. Day 1 or Day 5 in both the 1 mg and 3 mg dose groups, but not in 2 mg group (day effect). The median percent change for intraesophageal AUC for Day 1 (Day 1 as percentage of Day 5) for 1 mg, 2 mg and 3 mg were 84.60%, 48.66% and 99.23% respectively. Neither the day effect (comparison of Days 1 or 5 of dosing with baseline Day-1 within each dose group) nor the dose effect (comparison of dose groups 1 mg, 2 mg, and 3 mg within each day's test) showed statistically significant differences in the % time intraesophageal pH<4.0. There were also no differences in the frequency of reflux events between days within dose groups or between dose groups on Days 1 and Day 5 of dosing. However, when comparing frequency of prolonged reflux events, the 3 mg dose group started with a significantly higher baseline number of events compared to the 1 mg group, and showed a statistically significant decrease (day effect) by pairwise comparison between Day 1 vs. Day -1 and Day 5 vs. Day -1. No such day effect was demonstrated in the 1 mg or 2 mg dose groups. **Safety**: • All of the subjects enrolled into the study (69 subjects) were included in the safety analysis set. • One death (judged as unrelated to the study drug) was reported in the rabeprazole 3 mg group and a total of 7 subjects (2 subjects in the rabeprazole 1 mg group, 1 subject in the rabeprazole 2 mg group and 4 subjects in the rabeprazole 3 mg group) experienced at least 1 serious adverse event. Included in this group is 1 subject in the 3mg group with necrotizing enterocolitis. • A total of 36 (52.2%) of the 69 subjects reported at least 1 treatment emergent adverse event (TEAE) with 42.1%, 48.0% and, 64.0% reported in the rabeprazole 1 mg, 2 mg and 3 mg dose groups, respectively. The most commonly occurring TEAEs by system organ class (SOC) were Blood and Lymphatic system disorders dominated by anemia (21.7%), followed by Infections and Infestations (18.8%), Gastrointestinal Disorders (15.9%), Eye Disorders (14.5%), and Respiratory, and Thoracic and Mediastinal Disorders (11.6%). AEs that occurred in more than 5% of subjects included anemia (18.8%), apnea (8.7%), bradycardia (7.2%), conjunctivitis (5.8%), and retinopathy of prematurity (5.8%). • There were no clinically relevant posttreatment abnormalities in the clinical laboratory test results except for 1 subject in rabeprazole 2 mg group who was observed with decreased hemoglobin and hematocrit values along with decreased red blood cell count as TEAE.

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