1. STUDY SYNOPSIS

Title of Study: Safety and Efficacy of Rabeprazole in the Treatment of Gastroesophageal Reflux Disease in 12-16 Year Old Subjects

Investigators: There were 25 investigators participating in this study. A complete listing is provided in Appendix 16.1.4.

Study Centers: 58

Publication(s): N/A

Studied Period: 18-AUG-2005 to 01-MAY-2006

Clinical Phase: II

Objectives:
The primary objective was to collect safety information on rabeprazole 10 mg and 20 mg in the treatment of gastroesophageal reflux disease (GERD) in children 12 to 16 years old.

The secondary objectives were to assess the efficacy of rabeprazole on the improvement of the symptoms of GERD and to explore the relationship of symptom relief to dose received based on symptom frequency and severity, antacid use, and quality of life (QOL) measures.

Methodology: This was a multicenter, open-label, randomized, parallel-group study conducted in 111 subjects. Subjects were between 12 to 16 years of age with a clinical diagnosis of symptomatic GERD or suspected or endoscopically proven GERD. Subjects were randomly assigned to receive either 10 mg or 20 mg rabeprazole (54 and 57 subjects per 10-mg and 20-mg group, respectively) once daily at the same time each day for 8 weeks, with a follow-up visit off study drug at Week 10. The duration of the study treatment was 8 weeks and the subjects’ participation in the study lasted up to 12 weeks including the screening phase and the 2-week post study drug follow-up.

Assessments included full physical examinations at Screening, Baseline (if more than 72 hours after Screening) and Week 8. A routine physical was performed at Week 10/Discharge; vital signs (sitting blood pressure and pulse, respiratory rate, and temperature) were taken at the biweekly study center visits; and changes in physical status since the previous study center visit or previous phone contact (each subject was called every other week to check compliance with the daily medication and symptoms diary, and AE assessments in the weeks where there were no study center visits) were assessed.

Weight and clinical laboratory samples (hematology, clinical chemistry, and urinalysis) were collected at Screening and Week 8 (laboratory evaluations were repeated at Baseline if the Screening Visit was greater than 72 hours before the Baseline Visit). Medical history and frequency and severity of GERD symptoms (experienced during the previous 2 weeks) were assessed at Screening.

Beginning at Screening, subjects recorded the frequency and severity of 5 predetermined GERD symptoms (‘heartburn’, ‘regurgitation’, ‘nausea’, ‘vomiting’, and ‘epigastric pain’) and up to 2 other subject-selected GERD symptoms chosen during the Screening Visit from a list which included but was not limited to ‘cough’, ‘belching’, ‘fullness’, ‘abdominal pain’, ‘anorexia’, ‘hoarseness’, ‘dysphagia’, ‘abdominal distension’, ‘painful swallowing’, ‘wheezing’, ‘choking’, ‘chest pain’, as well as general gastrointestinal symptoms of ‘flatulence’, ‘constipation’, and ‘diarrhea’. Symptom severity was determined through a 5-point Likert scale, which subjects used to rate how bothered they were by each symptom.

At the biweekly study center visit, a quality of life (QOL) assessment was conducted using the Medical Outcomes Study 10-item Short form questionnaire (SF-10) and the Psychological General Well-Being Index (PGWBI) scales. GERD symptoms were evaluated at the biweekly study center visits by having the subjects answer the GERD Symptom Assessment questionnaire (GSAS, version 4) along with a Visual Analog Scale called Pain Faces for each item on the GSAS questionnaire.

Subjects were asked the following overall symptom assessment question on symptomatic response to treatment at the end of active study drug treatment (Week 8, or when the subject prematurely discontinued the study): “Overall, how would you rate the severity of your symptoms during the past 8 weeks?: No Symptoms, Very mild, Mild, Moderate, Severe, Very severe.” (Note: This QOL question and response options deviated from the protocol. The symptomatic response to treatment for baseline was compared to 8 weeks and these derived data were presented in Table 14.2.2.14.)

Number of Subjects: A total of 111 subjects were enrolled and 107 subjects completed the study. Data for safety analysis were available from 111 subjects. Data for efficacy analysis were available from 111 subjects.

Diagnosis and Criteria for Inclusion: Subjects aged 12 to 16 years with a clinical diagnosis of symptomatic GERD or suspected or endoscopically proven GERD were eligible to participate in the study.

Subjects who had been treated with proton pump inhibitors (PPIs), H2-blockers or antacids were eligible as long as they discontinued PPIs and H2 blockers at least 3 days before study drug administration. Cimetidine must have been discontinued for at least 7 days before study drug dosing. Additionally, subjects should have been able to have a 2 week PPI therapy-free period at the end of active study drug treatment. Subjects with a history of primary esophageal motility disorders or systemic condition affecting the esophagus (eg, scleroderma, esophageal infections), or eosinophilic esophagitis, persistent milk protein allergy, allergic gastroenteropathy, history or current presence of peptic ulcers, current presence of Helicobacter pylori, definitive acid-lowering surgery, previous esophageal surgery, or esophageal stricture were ineligible for this study.

Test Product: Rabeprazole sodium (E3810, AcipHex®)

Dose: 10-mg and 20-mg enteric-coated tablets

Mode of Administration: oral, once per day
Duration of Treatment: The study duration was up to 12 weeks including a screening evaluation within 2 weeks prior to study drug administration (Week -2 to 0). Eight weeks of active drug treatment (Week 0 to Week 8) and a follow-up visit 2 weeks later (Week 10).

Reference Therapy, Dose, Mode of Administration, Batch No(s): N/A

Criteria for Evaluation: The safety of rabeprazole after daily dosing at either 10 mg or 20 mg for 8 weeks was evaluated based on incidence of treatment emergent adverse events (AEs), clinical laboratory values, and physical examinations. The efficacy of rabeprazole was evaluated based on change in frequency and severity of GERD symptoms, change in antacid use, and change in QOL compared to baseline and exploration of dose received to symptom response.

Statistical Methods: A Safety population (all subjects who received at least 1 dose of study treatment) and Intent-to-Treat (ITT) population (all subjects in the safety population who also had at least 1 postbaseline assessment) were identified for this study. In addition, a subset of the ITT population, the Per-Protocol (PP) population (included those subjects in the ITT population who were study drug compliant [ie, took at least 80% of planned doses as determined by pill count] and diary compliant [ie, at least 80% of daily recordings filled out on the appropriate day as determined by study center]) was also identified. The Safety population was the primary analysis population and the ITT and PP populations were the efficacy analysis populations.

The demographic and baseline characteristics (age, gender, race, height, weight, vitals [blood pressure and pulse, body respiratory rate, and temperature], and screening physical examinations) were summarized descriptively by treatment group, including total number of subjects (N), mean, median, standard deviation (SD), and range for the Safety population and ITT population. For continuous variables, ANOVA with treatment and center as fixed factors were used to compare demographic and baseline characteristics of the two treatment groups. Cochran-Mantel-Haenszel test stratified by center was used for categorical variables.

Efficacy variables (frequency and change in frequency of GERD symptoms, frequency and change in severity of GERD symptoms, antacid use, QOL assessment from baseline throughout study, and symptom response at Weeks 8 and 10) were tabulated and summarized descriptively based on predose and postdose values for the two treatment groups and overall.

Hypothesis testing of efficacy parameters was conducted for exploratory purposes and P-values were calculated without multiplicity adjustment for multiple endpoints. The hypothesis that GERD symptom frequencies and severity, antacid use, and QOL scores would show improvement postdose and at Week 10 versus Week 8 was tested using paired t-tests for continuous and ordinal variables. The difference between the rabeprazole 10-mg dose and 20-mg dose on efficacy measures was tested using ANOVA or ANCOVA for continuous and ordinal variables and the Cochran-Mantel-Haenszel test or logistic regression was applied for binary variables. A P-value of < 0.05 indicated a significant difference between the two treatment groups in the parameter of interest.

Safety analyses were performed on the Safety population. For all treated subjects, the parameters related to the extent of exposure were summarized by treatment group using descriptive statistics. The incidence of AEs was summarized by body system, Medical Dictionary for Regulatory Affairs (MedDRA) preferred term, and treatment group. All AEs were analyzed using descriptive statistics. Clinical laboratory results (hematology, clinical chemistry, and urinalysis) were summarized descriptively, including summary tables to show changes from baseline to Week 8. Shift tables summarizing number and percentage for shift of laboratory measurements from normal to abnormal (ie, low or high) and abnormal to normal were also produced.

Vital signs were summarized by treatment group and by visit (Screening, Baseline, Week 2, Week 4, Week 6, Week 8, and Week 10), and change from baseline values by treatment and by visit (Weeks 2, 4, 6, 8, and 10) were summarized. In addition, weight change from Screening (or baseline if Baseline Visit was within 72 hours of the Screening Visit) to Week 8 was descriptively analyzed for the safety population. Summary statistics also included the median at baseline and the median change from baseline at each visit (Week 2, Week 4, Week 6, Week 8, and Week 10). A general linear model with treatment and center as fixed factors was used.

SUMMARY – CONCLUSIONS:

RESULTS:

Efficacy: As the primary objective of this study was to collect safety information, no placebo arm was used in this study design. Most of the endpoints were summarized by descriptive statistics to compare postdose against the baseline values as well as between 10-mg and 20-mg dose levels. The efficacy endpoints for this study included the change in frequency and severity of 5 primary GERD symptoms (‘heartburn’, ‘regurgitation’, ‘nausea’, ‘vomiting’, and ‘epigastric pain’, and 2 additional subject-selected symptoms if present), change in antacid use, and the change in QOL (PGWB1 and SF-10) from baseline, as well as the exploration of dose received to symptom response. P-values reported as statistically significant (ie, P-values < 0.05) were not adjusted for multiplicity and therefore should be interpreted with caution.

In general, the mean frequencies of GERD symptoms reported at Week 8 were lower than at baseline in both dosing groups for all symptoms. Similarly, decreases in the frequency of GERD symptoms were observed at Week 10 compared to baseline in both dosing groups for all symptoms. The largest improvements in GERD symptoms were seen for the symptoms ‘Other’ (symptoms chosen by the subjects at screening from a list of 20, if present [refer to Methodology Section for partial list]) at daytime followed by ‘heartburn’ at daytime. When mean symptom frequencies reported at Week 10 were compared to Week 8, Week 10 continued to show improvement from baseline, however the improvements were not as great.
as those seen at Week 8 for most symptoms. The 20-mg treatment group showed greater improvements than the 10-mg treatment group on most GERD symptoms, though not statistically significant.

The severity of the symptoms, based on mean Likert scores from the daily diaries, were consistently improved from baseline to post-baseline visits, often with the largest improvement observed at Week 8. The 20-mg treatment group tended to have greater improvements in the severity of GERD symptoms as compared to the 10-mg group, but the differences were mostly not statistically significant.

No large differences in antacid use were reported during the study as compared to baseline in either population (ITT and PP populations) based on the answers to the question “Did the subject take 6 or fewer antacids per day on average?” In addition, there did not appear to be a difference in response to this question between the two dose groups.

Responses to the QOL questionnaires (PGWBI and SF-10) showed consistent and mostly significant (ie, P-values < 0.05 without adjusting for multiplicity) improvements over baseline in both the ITT and PP populations. Based on the PGWBI questionnaire, significant improvements from baseline were observed on the dimensions of anxiety, depressed mood, positive well-being, self control, general health, vitality and the raw index score. There were also significant differences observed between the 10-mg and 20-mg dose groups at one or more visits on the dimensions of depressed mood, positive well-being, vitality and raw index score, with the 20-mg dose group showing greater improvement from baseline as compared to the 10-mg group. Based on the SF-10 questionnaire, significant improvements from baseline to each timepoint through Week 10 were observed in mean physical summary scores in both dose groups (ITT and PP populations). The mean psychological summary scores from the SF-10 questionnaire showed significant improvements from baseline at post-baseline visits in the 10-mg dose group (ITT and PP populations). The change in mean psychological summary score for the 20-mg dose group only showed significant improvement from baseline at Week 6 in the ITT population and Weeks 6, 8, and 10 in the PP population.

Improvements from baseline to post-baseline visits based on pain (VAS) scores, number of GERD symptoms, frequency count, and Likert distress scores were observed for most of the 15 GERD symptoms on the GSAS questionnaire. Improvement in overall severity of GERD symptoms was also observed as measured on a biweekly basis. Finally, responses to the overall GERD assessment question at Week 8 showed that most subjects, 28.8% and 44.2% in the 10-mg dose group and 28.3% and 39.6% in the 20-mg dose group, felt completely or somewhat relieved of their GERD symptoms, respectively. There were few differences observed in improvement in GSAS responses between the 10-mg and 20-mg dose groups for most parameters, except a few components with P-values < 0.05 (without adjustment for multiplicity).

In summary, subjects in this study consistently experienced improvements in GERD symptom frequency and severity as measured by daily diary entries and GSAS questionnaire responses, and in quality of life as measured by responses to the PGWBI and SF-10 questionnaires. There were no large changes in antacid use by the subjects while on the study drug. There were few differences in improvement between the 10-mg and 20-mg dosing groups for most of the parameters examined, except for a few components with P-values < 0.05 (without adjustment for multiplicity). Clinical improvement in GERD symptoms persisted during the follow-up period (Week 10), but these improvements were not as great as those observed at Week 8. Improvements in QOL questionnaire responses persisted through follow-up (Week 10).

**Safety:** Adverse events were reported in 31 of 54 (57.4%) subjects in the 10-mg dose group and in 35 of 57 (61.4%) subjects in the 20-mg dose group. Most of the events in each group were mild to moderate in severity. A total of 8 of 54 (14.8%) subjects in the 10-mg dose group and 8 of 57 (14.0%) subjects in the 20-mg dose group experienced events that were possibly or probably related to the study drug. AEs reported in ≥ 5% (corresponding to three or more subjects) of the subjects in either treatment group were pharyngolaryngeal pain, headache, cough, upper respiratory tract infection, nasal congestion, nasopharyngitis, diarrhea, nausea, bronchitis, pharyngitis, abdominal pain upper, chest pain, otitis media, and sinusitis. One SAE, mood swings, was reported and was considered not related to rabeprazole by the investigator. No subject discontinued from the study due to AEs and there were no deaths reported in the study.

There were only a few clinically significant changes in laboratory values. There were no patterns to suggest a clinically relevant effect of the study drug on clinical laboratory values. Statistically significant changes between baseline and post-baseline visits for vital signs and weight were not considered clinically significant.

The results of this study indicate that 10 mg and 20 mg of rabeprazole administered daily to 12 to 16 year old subjects with GERD for 8 weeks was safe and well tolerated.

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<thead>
<tr>
<th>Adverse Events Reported with Highest Incidence (≥5%)</th>
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<tbody>
<tr>
<td>Treatment Emergent AEs (Number (%) Subjects)</td>
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<tr>
<td>Treatment Emergent AEs (Possibly or Probably Related to Study Drug) (Number (%) Subjects)</td>
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<tr>
<td>System Organ Class and MedDRA Preferred Term</td>
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<tr>
<td>Gastrointestinal Disorders:</td>
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<tr>
<td>Abdominal Pain Upper</td>
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<td>Diarrhea</td>
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## Adverse Events Reported with Highest Incidence (≥5%)

<table>
<thead>
<tr>
<th>System Organ Class and MedDRA Preferred Term</th>
<th>Treatment Emergent AEs Number (%) Subjects</th>
<th>Treatment Emergent AEs (Possibly or Probably Related to Study Drug) Number (%) Subjects</th>
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<tbody>
<tr>
<td>Rabeprazole 10 mg</td>
<td>Rabeprazole 20 mg</td>
<td>Rabeprazole 10 mg</td>
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<tr>
<td>N=54</td>
<td>N=57</td>
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<tr>
<td>Nausea</td>
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<td>3 (5.6)</td>
<td>2 (3.5)</td>
<td>1 (1.9)</td>
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<td>General Disorders and Administration Site Conditions:</td>
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<tr>
<td>Chest Pain</td>
<td>0 (0.0)</td>
<td>3 (5.3)</td>
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<td>Infections and Infestations:</td>
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<tr>
<td>Bronchitis</td>
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<tr>
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<td>4 (7.0)</td>
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<td>Headache</td>
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<td>Pharyngolaryngeal Pain</td>
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Source: Tables 14.3.1.2 and 14.3.1.4 / Section 14.3

### CONCLUSIONS:

- Rabeprazole 10 mg and 20 mg administered once daily to 12 to 16 year old subjects with GERD for 8 weeks was safe and well tolerated.
- Rabeprazole 10 mg and 20 mg administered once daily improved the symptoms of GERD in 12 to 16 year old subjects based on symptom frequency and severity and quality of life measures. Antacid use as measured in this study remained generally unchanged from baseline.
- There did not appear to be large differences between results in the 10-mg dose group as compared to the 20-mg dose group in most measures.

Date of the Report: 04-MAY-2007