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A multicentre, randomized, open-label Phase IV study exploring symptom control rate in co-diagnosed NERD and chronic gastritis patients treated with 8 weeks esomeprazole treatment regimen and 2 weeks esomeprazole treatment regimen

Study dates: First subject screened: 14 April 2010
Last subject last visit:01 June 2011

Phase of development: IV

Sponsor's Responsible Medical Officer: Karen Atkin

This study was performed in compliance with Good Clinical Practice, including the archiving of essential documents.

Study Centres

Patients were enrolled at 10 centres in the People's Republic of China.

Publications

None at the time of writing this report.

Objectives and Criteria for Evaluation

Primary:

- To compare the symptom control rates at 24 weeks maintenance treatment/follow-up between 8 weeks esomeprazole treatment group and 2 weeks esomeprazole treatment group in co-diagnosed NERD (non- erosive reflux disease) and chronic gastritis patients, as evaluated by GerdQ at 24 weeks maintenance treatment/follow-up. Here symptom control is defined as patients with all the items ≤1 in A and C categories of GerdQ.

Secondary:

- To compare the success rates between 8 weeks esomeprazole treatment group and 2 weeks esomeprazole treatment group in co-diagnosed NERD and chronic gastritis patients. Success is defined as patients with symptom relief after 8 weeks or 2 weeks esomeprazole treatment, and also achieved symptom control at 24 weeks maintenance treatment/follow-up period.

- To assess time to first relapse, defined as the period from the date of last dose of the 8 weeks or 2 weeks treatment regimen to the date of first time patient comes to see the investigator due to symptom relapse.

- To assess symptom control rates at 8 and 16 weeks visits in 24 weeks maintenance treatment/follow-up period, as evaluated by GerdQ.

- To assess the symptom relief rates at the end of 8 weeks or 2 weeks esomeprazole treatment regimens. Here symptom relief is defined as no more than one day with mild symptoms of GERD during the previous 7 days.

- In the 8 weeks treatment group, to compare the symptom relief rates after 2weeks and 8 weeks treatment.

- To compare the number of unscheduled hospital visits between the two different treatment groups during the 24-week maintenance treatment/follow-up period.

- To measure patient satisfaction in the two different treatment groups.

Study Design

This was a randomized, open-label study designed to be naturalistic in accordance with how patients were treated in clinical practice in China.

Patients with endoscopically diagnosed chronic gastritis (non-atrophic and mild atrophic gastritis) and GerdQ Score$\geq$ 8 were randomized into two groups.

One group was the 8 weeks treatment group, where patients received esomeprazole 20 mg qd treatment for 8 weeks, and the patients with symptom relief (defined as no more than one day with mild symptoms of GERD during the previous 7 days) were to receive another 24 weeks on-demand maintenance treatment. The 8 weeks treatment regimen is the NERD standard symptomatic treatment recommended by China GERD consensus (Chinese Medical Association, 2007).

The second group was the 2 weeks treatment group, where patients received 2 weeks esomeprazole 20 mg qd treatment, and, if symptom relief was achieved, would enter 24 weeks follow-up period. During the follow-up period, if the patients had symptom recurrence and needed treatment in the opinion of investigator, they would be given another 2-week esomeprazole 20 mg qd as recurrent treatment, and there was no limitation for the number of repeated 2 week treatments in 24 weeks follow-up period.

The patients without symptom relief after 8 weeks treatment in 8 weeks treatment group or after 2 weeks treatment in 2 weeks treatment group were to be withdrawn from the study and treated according to clinical routines.

There were three scheduled visits (at 8, 16 and 24 weeks) in the 24 weeks on-demand maintenance treatment/follow-up period. Any unscheduled visits were indicated by the recurrence of the patient's symptoms, need for extra treatment, or need for medical consultation.

GerdQ was assessed when the patients entered the study and at 8, 16 and 24 weeks visits in maintenance treatment/follow-up period to assess the symptom control in two groups. Patients with symptom control were defined as patients with all the items ≤ 1 in A and C categories of GerdQ. The symptom control rates were compared between the two treatment groups at the three scheduled visits (8, 16 and 24 weeks in 24 weeks maintenance treatment/follow-up period).

Target Subject Population and Sample Size

The target subject population were those who were endoscopically diagnosed with chronic gastritis (non-atrophic and mild atrophic gastritis) with GerdQ score ≥ 8.

Since we did not have previous data for the symptom control rates in the two treatment regimens, the sample size was calculated based on clinical experience. With a total of 170 evaluable patients, 85 in the 8 weeks treatment group and 85 in the 2 weeks treatment group, the power would be over 80% to detect a difference of 20% in symptom control rates between two treatment groups at two-sided significance level of 0.05 using Fisher exact test, assuming the symptom control rates around 66% in 2 weeks treatment group and 86% in 8 weeks treatment group (based on data from BU-NEG-0005 study). Considering the PPI response rates of around 70% and the drop-out rates of around 20%, approximately 300 patients were needed to be randomised.

Investigational Product Dosage Form and Strength, and Manufacturer

Esomeprazole 20 mg tablet Astrazeneca AB, Sweden

Duration of Treatment

8 weeks treatment group:

The total duration was 32 weeks, including 8 weeks esomeprazole treatment and 24 weeks on-demand maintenance treatment.

2 weeks treatment group:

The total duration was 26 weeks, including 2 weeks esomeprazole treatment and 24 weeks follow-up. During the follow-up period, if the patients' symptoms recurred and needed treatment in the opinion of investigator, they would be given another 2-week esomeprazole 20 mg qd as recurrent treatment. There was no limitation for the number of repeated 2 week treatments in the 24-week follow-up period.

Statistical Methods

Analysis on efficacy endpoints was performed for intention to treat (ITT) population, modified intention to treat (MITT) population and per protocol (PP) population, with MITT as the primary analysis population.

ITT was defined as all randomized subjects who took at least one dose of treatment. MITT was defined as patients in ITT population with symptom relief after 8 weeks or 2 weeks esomeprazole treatment. Efficacy analysis was also repeated in per protocol (PP) population

including ITT-PP and MITT-PP population, defined as all subjects without significant protocol violations/deviations out of ITT and MITT population respectively. Detailed criteria and identification of the Per Protocol population were decided in the statistical analysis plan prior to the database lock.

All treatment comparisons were 2-sided and the nominal level of significance was 5%.

In general, frequency tables (number and percentage of subjects) were used for categorical variables. Descriptive statistics (number, mean, median, standard deviation, minimum and maximum) were performed for continuous variables. Kaplan-Meier method was used to assess time to first relapse.

Statistical analysis of the primary endpoint was based on Fisher's exact test using the modified intention to treat (MITT) population.

Safety endpoints were summarized by treatment received in the safety population. No inferential statistical analysis was done for the safety variables. Descriptive statistics for SAEs and DAEs were performed.

Summary of Demographics, Other Baseline Characteristics, and Baseline Disease

Three hundred and five patients, out of the 311 patients who signed the informed consent, were randomized to receive 8 weeks (n=154) or 2 weeks (n=151) of esomeprazole treatment. Esomeprazole relieved symptoms in 136 patients in 8 weeks group and 126 patients in 2 weeks group. Accordingly, 305 patients and 262 patients were included into ITT and MITT population respectively.

With the exception that the ratio of females to males was greater in the 2 weeks regimen than in the 8 weeks regimen, other demographics including age, race and other baseline characteristics were well-balanced between the 2 weeks regimen and the 8 weeks regimen. Baseline disease status was also comparable between the two regimens.

Summary of Efficacy Results

Primary variable: Symptom Control Rate at 24 weeks Maintenance Treatment/ Follow-up

Based on the MITT population, the symptom control rate showed a statistical significant difference at 24 weeks maintenance/treatment follow-up visit in favor of the 8 weeks regimen as compared to the 2 weeks regimen（94.9% vs. 87.3%，P = 0.0473 by Fisher exact test). Symptom control rates were also consistently better with 8 weeks esomeprazole regimen at 8 weeks (80.1% vs. 75.4%, P=0.3748) and 16 weeks (85.3% vs. 80.2%, P=0.3258), as summarized in Table S1 for MITT.

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Table S1   **Symptom Control Rates at 24 weeks Maintenance Treatment/ Follow-up (MITT Population)**

	2 Weeks Regimen (N=126)	*8 Weeks Regimen (N=136)*
8 weeks		
Controlled	95 (75.4%)	109(80.1%)
Not Controlled	31 (24.6%)	27 (19.9%)
Treatment difference in symptom control rate		
8 Weeks Regimen - 2 Weeks Regimen	4.8%	
95% CI	-5.3%, 14.8%	
P value	0.3748	
16 weeks		
Controlled	101(80.2%)	116(85.3%)
Not Controlled	25 (19.8%)	20 (14.7%)
Treatment difference in symptom control rate		
8 Weeks Regimen - 2 Weeks Regimen	5.1%	
95% CI	-4.0%, 14.3%	
P value	0.3258	
24 weeks		
Controlled	110(87.3%)	129(94.9%)
Not Controlled	16 (12.7%)	7 (5.1%)
Treatment difference in symptom control rate		
8 Weeks Regimen - 2 Weeks Regimen	7.6%	
95% CI	0.7%, 14.4%	
P value	0.0473	

Note: The denominator of percentage is N.

Note: Fisher's exact test compared the symptom control rate between the 2 treatment regimens during 24 weeks of follow-up. Note: patients with symptom control are defined as patients with all items ≤ 1 in A and C categories (Questions 1, 2, 5 and 6) of GerdQ.

Secondary variables:

1. Success Rate in the Whole Study Duration

Analysis on the success rate demonstrated statistically significant better result with 8 weeks regimen than with 2 weeks regimen on both ITT (83.8% patients in 8 weeks regimen vs. 72.8% in 2 weeks regimen, P=0.0258) and ITT-PP populations, as summarized in Table S2.

Table S2   **Success Rate in the Whole Study Duration (ITT Population)**

	2 Weeks Regimen (N=151)	*8 Weeks Regimen (N=154)*
Success	110(72.8%)	129(83.8%)
Not Success	41 (27.2%)	25 (16.2%)
Treatment difference in symptom success rate		
8 Weeks Regimen - 2 Weeks Regimen	10.9%	
95% CI	1.7%, 20.1%	
P value	0.0258	

Note: The denominator of percentage is N.

Note: Fisher's exact test compared the symptom success rate between the 2 treatment regimens after 24 weeks of follow-up.

Note: Success is defined as patients with symptom relief after 8 weeks or 2 weeks esomeprazole treatment, and also get symptom controlled during maintenance treatment / follow-up period.

2. Time to first relapse

Table S3 presents a summary of time to first relapse in MITT population by treatment regimen.

A total of 126 patients on the 2 weeks regimen and 136 patients on the 8 weeks regimen were included in the survival analysis. Relapse free rate at fixed time point of 8 weeks, 16 weeks, and 24 weeks also have been computed and compared using Kaplan-Meier method (Klein J.P). Significantly more patients in 8 weeks stayed relapse free in the maintenance/follow up phase.(68.4% vs 50.6%, P=0.003 at week 8; 63.2% vs 44.1%, P=0.0016 at week 16; 56.3% vs. 36.6%, P=0.0012 at week 24)

Table S3   Time to First Relapse (MITT Population)

	2 Weeks Regimen (N=126)	*8 Weeks Regimen (N=136)*
No. of patients with relapse	80 (63.5%)	59 (43.4%)
No. of patients censored	46 (36.5%)	77 (56.6%)
Kaplan-Meier estimate of relapse free duration (days)		
Minimum*	2	3
25% percentile (95% CI)	12.0 (8.0 , 17.0)	35.5 (22.0 , 65.0)
Median (95% CI)	57.0 (41.0 , 124.0)	NA (149.0 , NA)
75% percentile (95% CI)	174.0 (174.0 , NA)	NA (NA , NA)
Maximum*	174	168
Relapse free rate		
8 weeks relapse free rate (95% CI)	0.506 (0.419, 0.594)	0.684 (0.606, 0.762)
Relapse free rate difference (8 weeks regimen - 2 weeks regimen) (95% CI)	0.178 (0.060, 0.295)	
Rate difference p value	0.0030	
16 weeks relapse free rate (95% CI)	0.441 (0.354, 0.528)	0.632 (0.551, 0.713)
Relapse free rate difference (8 weeks regimen - 2 weeks regimen) (95% CI)	0.191 (0.072, 0.310)	
Rate difference p value	0.0016	
24 weeks relapse free rate (95% CI)	0.366 (0.281, 0.451)	0.563 (0.479, 0.647)
Relapse free rate difference (8 weeks regimen - 2 weeks regimen) (95% CI)	0.197 (0.078, 0.317)	
Rate difference p value	0.0012	
Hazard ratio (95% CI)		0.543 (0.388, 0.761)
Log-Rank test		

* Minimum and maximum only applies to patients with relapse.

Note: The denominator of percentage is N.

Note: Time to first relapse is from the last dose during the treatment period to date of first time patient comes to the investigator due to symptom recur and need for treatment.

Note: Relapse free rate was estimated from survival analysis.

Note: Log-Rank Test compared the relapse free survival function between the 2 treatment regimens.

Note: Unadjusted HR (Hazard Ratio) from Cox model with treatment as the only explanatory factor. HR < 1.0 favors 8 weeks regimen.

3. Symptom Relief Rate in 2 Treatment Regimens

The symptom relief rate is summarized in Table S4 for ITT population. There were 136(88.3%) patients in 8 weeks regimen and 126(83.4%) in 2 weeks regimen respectively and the difference is not statistically significant (P =0.2513).

Table S4   Symptom Relief Rate in 2 Treatment Regimens (ITT Population)

	2 Weeks Regimen (N=151)	*8 Weeks Regimen (N=154)*
Relieved	126(83.4%)	136(88.3%)
Not Relieved	25 (16.6%)	18 (11.7%)
Treatment difference in symptom relief rate		
8 Weeks Regimen - 2 Weeks Regimen	4.9%	
95% CI	-2.9%, 12.7%	
P value	0.2513	

Note: The denominator of percentage is N.

Note: Fisher's exact test compared the symptom relief rate between the 2 treatment regimens.

Note: Symptom relief is defined as no more than 1 day of mild symptoms of GERD during previous 7 days after 8 weeks or 2 weeks of treatment.

4. Symptom Relief Rate after 2 Weeks and 8 Weeks in 8 Weeks Treatment Group

Within the 8 weeks regimen, there were 84 (54.5%) patients with symptom relief at 2 weeks and 136 (88.3%) at 8 weeks during treatment period, as shown in Table S5 for ITT population, which presented a statistically significant difference that suggests constant improvement in the symptom relief rate during the 8-week treatment period.

Table S5   Symptom Relief Rate after 2 Weeks and 8 Weeks in 8 Weeks Treatment Group (ITT Population)

	8 Weeks Regimen (N=154)
2 weeks	

No. of patients with symptom relief	84 (54.5%)
No. of patients without symptom relief	70 (45.5%)
8 weeks	
No. of patients with symptom relief	136(88.3%)
No. of patients without symptom relief	18 (11.7%)
Difference comparison of symptom relief rate	
8 weeks - 2 weeks	33.8%
95% CI	24.4%, 43.1%
P value	< 0.0001

Note: The denominator of percentage is N.

Note: Fisher's exact test compared the symptom relief rate between 2 weeks and 8 weeks of treatment period in 8 weeks regimen.

Note: Symptom relief is defined as no more than 1 day of mild symptoms of GERD during previous 7 days after 8 weeks or 2 weeks of treatment.

5. Number of Unscheduled Hospital Visits During the 24-week Maintenance Treatment/Follow-up Period

The analysis on the number of patients with unscheduled hospital visits are summarized in Table S6 for MITT population, where there were 59 (43.4%) for the 8 weeks regimen and 80 (63.5%) for 2 weeks regimen. The comparison of proportion of patients with unscheduled visits between 2 regimens showed a statistically significant difference favoring 8 weeks regimen with p-value of 0.0013.

Table S6   **Total Number of Unscheduled Hospital Visits During the 24-week Maintenance Treatment/Follow-up Period (MITT Population)**

	2 Weeks Regimen (N=126)	8 Weeks Regimen (N=136)	Total (N=262)
Number of patients with unscheduled visit(s)	80 (63.5%)	59 (43.4%)	139(53.1%)
Number of patients without unscheduled visit(s)	46 (36.5%)	77 (56.6%)	123(46.9%)
Difference in the proportion of patients with unscheduled visits			
8 Weeks Regimen - 2 Weeks Regimen	-20.1%		
95% CI	-31.9%, -8.3%		
P value (Fisher's exact test)	0.0013		
Total number of unscheduled visits(s)			
0	46 (36.5%)	77 (56.6%)	123(46.9%)
1	30 (23.8%)	31 (22.8%)	61 (23.3%)
2	24 (19.0%)	14 (10.3%)	38 (14.5%)
3	12 (9.5%)	7 (5.1%)	19 (7.3%)
4	6 (4.8%)	3 (2.2%)	9 (3.4%)
5	3 (2.4%)	2 (1.5%)	5 (1.9%)
6	3 (2.4%)	1 (0.7%)	4 (1.5%)
8	2 (1.6%)	1 (0.7%)	3 (1.1%)
Estimated number of unscheduled visits per patient	1.4841	0.8529	
P value	0.0009		

Note: The denominator of percentage is N.

Note: Regimen comparison of the proportion of patients with unscheduled hospital visit is performed with Fisher's exact test, and the number of unscheduled visits per patient was modeled by weighted least square regression using regimen as the only predictor.

6. Proportion of Patients Satisfaction

The proportion of patients with satisfaction after 24 weeks of follow-up in the 8 weeks regimen was 100% while that of the 2 weeks regimen was 96% with a p-value of 0.0247 (Table S7) favoring 8 weeks regimen. Proportion of very satisfied after 24 weeks of follow-up were 24.6% and 48.5% for 2 weeks regimen and 8 weeks regimen respectively and Fisher exact test showed a strong statistical significance (p-value 0.0001) favoring 8 weeks regimen.

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Table S7   **Proportion of Patient Satisfaction During Follow-Up (MITT Population)**

	2 Weeks Regimen (N=126)	8 Weeks Regimen (N=136)	Total (N=262)	Fisher Exact Test p-Value
Satisfied				
After 8 weeks	114(90.5%)	133(97.8%)	247(94.3%)	0.0148
After 16 weeks	111(88.1%)	133(97.8%)	244(93.1%)	0.0025
After 24 weeks	121(96.0%)	136(100.0%)	257(98.1%)	0.0247
Very satisfied				
After 8 weeks	26 (20.6%)	69 (50.7%)	95 (36.3%)	< 0.0001
After 16 weeks	33 (26.2%)	63 (46.3%)	96 (36.6%)	0.0008
After 24 weeks	31 (24.6%)	66 (48.5%)	97 (37.0%)	0.0001

Note: The denominator of percentage is N.

Note: Satisfied - satisfaction score of 1-4 while very satisfied - satisfaction score of 1-2.

Summary of Safety Results

The drug exposure was different for the two treatment regimens. Only SAEs and DAEs were collected. No SAEs or deaths were observed. Generally the study drug was well-tolerated, with most of the reported DAEs being GI DAEs with mild or moderate severity. The number of DAEs was similar across the two treatment regimens.