Drug Product	Nexium	**SYNOPSIS**	
Drug Substance	Esomeprazole		
Study Code	D961DL00004		
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A randomised, double-blind, double-dummy, parallel-group, active-controlled, multicenter study to assess the efficacy and safety of esomeprazole 40 mg q12h i.v. or omeprazole 40 mg q12h iv administration for 5 days in subjects with acute non-variceal upper gastrointestinal bleeding

Study centre(s)

This study was conducted in China (13 centres)

Publications

None at the time of writing this report

Study dates		**Phase of development**
First subject enrolled	28 August, 2006	Therapeutic confirmatory (III)
Last subject completed	28 Oct. 2007	

Objectives

Primary objective

- To evaluate the efficacy of esomeprazole 40 mg q12h or omeprazole 40 mg q12h as a 30-minute infusion for 5 days in subjects with acute non-variceal upper gastrointestinal bleeding by assessment of proportion of subjects who present with no clinically significant upper GI bleeding after 5-day treatment.

Secondary objectives

To evaluate the efficacy and safety of esomeprazole 40 mg q12h or omeprazole 40 mg q12h as a 30-minute infusion in subjects with acute non-variceal upper gastrointestinal bleeding by assessment of:

- Proportion of subjects who present with no clinically significant upper GI bleeding after 72-hour treatment
- Time to absence of clinically significant upper GI bleeding
- Proportion of subjects who have surgery due to upper gastrointestinal bleeding within 5 days
- Number of blood units transfused within 72 hours and 5 days
- Safety and tolerability of esomeprazole and omeprazole

Study design

This study was a multi-center, randomized, double blind, double dummy, parallel-group, active-controlled non-inferiority study to assess the efficacy and safety of esomeprazole 40 mg q12h infusion or omeprazole 40 mg q12h infusion for 5 days in subjects with acute non-variceal upper gastrointestinal bleeding. In total 448 patients with acute non-variceal upper gastrointestinal bleeding, verified by endoscopies at baseline, were randomized in 13 centers.

Target subject population and sample size

Male and female subjects, 18-65 years who have overt signs of acute non-variceal upper gastrointestinal bleeding (melena and/or fresh hematemesis) within 48 hours, verified by endoscopies at baseline, were enrolled in this study.

The regulatory requirement was to have at least 300 patients in the esomeprazole treatment group and at least 80% power for a non-inferiority study. In addition, the Per Protocol (PP) population is assumed to be around 90% of the randomised patients. With planned 330 patients randomised to the esomeprazole group and 110 to the omeprazole group we can expect to have at least 300 and 100 patients, respectively, in the PP analysis set which gives a power of more than 80%.

446 evaluable subjects from 448 randomization, derived from 337 from esomeprazole group and 109 from omeprazole group, were required to investigate the proportion of no clinically significant upper GI bleeding after 5-day treatment between two treatment groups. Two randomized subjects from Omeprazole group were not considered as the evaluable ones because one was not dosed and another one randomized twice.

Investigational product and comparator(s): dosage, mode of administration and batch numbers

Esomeprazole powder for solution for infusion 40 mg, 30-minute infusion at every 12 hours, batch number was H 1516-03-02

Omeprazole powder for solution for infusion 40 mg, 30-minute infusion at every 12 hours, batch number was H 1489-01-01

Duration of treatment

Eligible subjects were treated for 5 days.

Criteria for evaluation (main variables)

Efficacy

- Primary variable: Proportion of subjects who present with no clinically significant upper GI bleeding after 5-day treatment.
- Secondary variables:
  - Proportion of subjects who present with no clinically significant upper GI bleeding after 72-hour treatment
  - Time to absence of clinically significant upper GI bleeding, by monitoring GI bleeding signs hourly in the first 12 hours of treatment and every 4 hours thereafter until no continuously bleeding signs detected
  - Proportion of subjects who have surgery due to upper gastrointestinal bleeding within 5 days
  - Number of blood units transfused within 72 hours and 5 days

Safety

- Adverse events, clinical laboratory findings, physical examination, vital signs, including blood pressure and pulse, ECG

Statistical methods

For the primary efficacy endpoint, the proportion of subjects who present no clinically significant upper GI bleeding after 5-day treatment was summarized and analyzed for both ITT (intention-to-treat) and PP (per protocol) population and the associated 2-sided 95% confidence intervals was calculated for each treatment group. Non-inferiority was claimed that the lower bound of the two-sided 95% confidence interval for the difference in the rate of no clinically significant upper GI bleeding was larger than –9.5% (10% of assumed effective rate –95%, defined by principal investigator) in the PP analysis. Data for safety variables was summarized descriptively by treatment received in the safety population.

Subject population

Subject population and disposition were summarized in Table S 1. In this table, demographic and baseline characteristics data are summarized from the safety population.

Table S 1 Subject population and disposition

		Esomeprazole		Omeprazole		Total	
Population							
N randomised (N planned)		337	(330)	111	(110)	448	(440)
Demographic characteristics[a]							
Sex (n and % of subjects)	Male	261	(77.4)	93	(85.3)	354	(79.4)
	Female	76	(22.6)	16	(14.7)	92	(20.6)
Age (years)	Mean (SD)	41.1	(13.4)	42.5	(12.9)	41.4	(13.3)
	Range	17 to 66		18 to 66		17 to 66	
Race (n and % of subjects)	Oriental	337	(100)	109	(100)	446	(100)
Baseline characteristics[b]							
BMI	Mean (SD)	22.74	(3.25)	22.90	(3.02)	22.78	(3.19)
Pulse rate(beats/ min)		82.1	(11.7)	80.3	(9.7)	81.7	(11.3)
Systolic BP (mmHg)		113.8	(15.3)	113.3	(13.5)	113.6	(14.9)
Diastolic BP (mmHg)		71.2	(10.7)	71.6	(10.1)	71.3	(10.6)
Hemoglobin (g/L)		106.6	(28.3)	109	(28.1)	107.2	(28.3)
Platelets Counts (10 *9/L)		191.4	(56.1)	202.1	(58.6)	194.0	(56.8)
Disposition							
N (%) of subjects who	Completed	321	(95.3)	108	(97.3)	429	(95.8)
	Discontinued	16	(4.7)	3	(2.7)	19	(4.2)
N analysed for safety[c]		337		109		446	
N analysed for efficacy (ITT)		337		109		446	
N analysed for efficacy (PP)		314		101		415	

[a,b] Data of demographic and baseline characteristics are based on the ITT population
[c] Number of subjects who took at least 1 dose of study treatment
ITT=Intention to treat; N=Number; PP=Per-protocol

451 subjects had been enrolled and 448 had been randomized. The treatment groups were generally well balanced in demographic and baseline characteristics. There were slightly fewer female in Omeprazole treatment group. The mean values of hemoglobin and platelets counts at baseline in Esomeprazole treatment group were slightly lower than those in Omeprazole group. Reasons of all discontinuations of study treatment or assessment were violation of inclusive / exclusive criteria (4 cases), safety reason (3 cases), severe upper GI

bleeding needing endoscopic therapy (1 case), unwilling to continue the study (6 cases) and other reasons stopped by the investigators (5 cases).

Table S 2 Endoscopic examination at baseline in ITT analysis set

		Esomeprazole (n= 337)		Omeprazole (n=109)		Total (n=446)	
		n	(%)	n	(%)	n	(%)
Esophagus							
Bleeding		0	(0)	0	(0)	0	(0)
Erosion		11	(3.3)	1	(0.9)	12	(2.7)
Other abnormity		25	(7.4)	8	(7.3)	33	(7.4)
Stomach							
Ulcer		24	(7.1)	12	(11)	36	(8.1)
Bleeding ulcer		50	(14.8)	29	(26.6)	79	(17.7)
Forrest Classification	Ia	0	(0)	0	(0)	0	(0)
	Ib	5	(1.5)	4	(3.7)	9	(2.0)
	IIa	5	(1.5)	0	(0)	5	(1.1)
	IIb	11	(3.3)	9	(8.3)	20	(4.5)
	IIc	3	(0.9)	5	(4.6)	8	(1.8)
	III	26	(7.7)	11	(10.1)	37	(8.3)
Erosion		69	(20.5)	24	(22)	93	(20.9)
Blood in the stomach		41	(12.2)	11	(10.1)	52	(11.7)
Other abnormity		165	(49)	54	(49.5)	219	(49.1)
Duodenum							
Ulcer		41	(12.2)	11	(10.1)	52	(11.7)
Bleeding ulcer		288	(85.5)	81	(74.3)	369	(82.7)
Forrest Classification	Ia	2	(0.6)	0	(0)	2	(0.4)
	Ib	59	(17.5)	13	(11.9)	72	(16.1)
	IIa	29	(8.6)	4	(3.7)	33	(7.4)
	IIb	68	(20.2)	15	(13.8)	83	(18.6)
	IIc	14	(4.2)	5	(4.6)	19	(4.3)
	III	116	(34.4)	44	(40.4)	160	(35.9)
Erosion		10	(3.0)	6	(5.5)	16	(3.6)

Table S 2 Endoscopic examination at baseline in ITT analysis set

	Esomeprazole (n= 337)		Omeprazole (n=109)		Total (n=446)	
	n	(%)	n	(%)	n	(%)
Other abnormity	25	(7.4)	8	(7.3)	33	(7.4)

Table S 3 Summary of Gastrointestinal History at baseline in ITT analysis set

	Esomeprazole (n= 337)		Omeprazole (n=109)		Total (n=446)	
	n	(%)	n	(%)	n	(%)
Gastric Ulcer	27	(8.0)	5	(4.6)	32	(7.2)
Duodenal Ulcer	97	(28.8)	27	(24.8)	124	(27.8)
Erosive Esophagitis	1	(0.3)	0	(0)	1	(0.2)
Previous Complication related with ulcer	72	(21.4)	22	(20.2)	94	(21.1)
Previous Hp Eradication therapy	0	(0)	0	(0)	0	(0)

For endoscopic finding, slightly more subjects of gastric bleeding ulcer in Omeprazole group and duodenal bleeding ulcer in Esomeprazole group were found. However the difference in Forrest class distribution at baseline is obvious, particularly for Forrest Ia and IIa grade, which imply the high risk for rebleeding. For Forrest Ia, there was no subject in Omeprazole group, while 2 subjects in Esomeprazole group. For Forrest IIa, more subjects in Esomeprazole group than Omeprazole group with 10.1% vs. 3.7% respectively. Conversely, more common was recorded for Forrest IIc and III in Omeprazole group with 59.7 % vs. 47.2% in Esomeprazole group, which imply the lower risk for rebleeding. Comparing with Omeprazole group, more subjects in Esomeprazole group had a history of gastric or duodenal ulcer.

Efficacy results

The primary endpoint, the proportion of no clinically significant upper gastrointestinal bleeding after 5 days treatment, exceeded 95% in both treatment groups in ITT population, with 95.3 % and 97.2 % in Esomeprazole group and Omeprazole group respectively. Esomeprazole group is non- inferior to Omeprazole group in subjects with acute non-variceal upper gastrointestinal bleeding. (p =0.3699) (See Table S 4) . Compared with ITT population, the result in PP population was similar with 97.1% vs 98% in Esomeprazole and Omeprazole treatment groups respectively (p=0.6297) (see Table S 5)

In terms of second efficacy results, no statistical significant differences were shown between two treatment groups. After 72 hours treatment, the proportion of no clinically significant

upper gastrointestinal bleeding in Esomeprazole and Omeprazole group were 87.2 % and 90.8 respectively (p=0.3146). The median time to absence of clinically significant upper gastrointestinal bleeding was same with 48 hours in both treatment groups (p=0.4161). One subject in Omeprazole group was needed surgery during the treatment period, while none in Esomeprazole group had this need (p=0.244). The median numbers of transfused blood units in Esomeprazole and Omeprazole group were 400 ml and 300 ml, respectively within both 5 days (p=0.1591) and 3 days (p=0.2127).

Table S 4 Proportion of No clinically significant upper GI bleeding after 5 days treatment (ITT population)

	Esomeprazole (N=337)		**Omeprazole (N=109)**		**P value**
	n (%)	**95% CI**	**n (%)**	**95% CI**	
No clinically significant upper GI bleeding after 5 day treatment	321 (95.3%)	(93.0, 97.5)	106(97.2%)	(94.2,100)	0.3699
Difference (Esomeprazole-Omeprazole) % **95% CI**	-2.0 (-6.4, 2.4)				

Table S 5 Proportion of No clinically significant upper GI bleeding after 5 days treatment (PP population)

	Esomeprazole (N=337)		Omeprazole (N=109)		P value
	n (%)	95% CI	n (%)	95% CI	
No clinically significant upper GI bleeding after 5 day treatment	305 (97.1%)	(95.3, 99)	99 (98 %)	(95.3, 100)	0.6297
Difference (Esomeprazole-Omeprazole) % **95% CI**	-0.9 (-4.8, 3.1)				

Safety result

Table S 6 Number (%) of subjects who had at least 1 adverse event in any category, and total numbers of adverse events (safety analysis set)

Category of adverse event	N (%) of subjects who had an adverse event in each category[a]					
	Esomprazole (N=337)		Omeprazole (109)		Total (N=446)	
Any adverse events	20	(5.9)	8	(7.3)	28	(6.3)
Serious adverse events	1	(0.3)	0	(0)	1	(0.2)
Serious adverse events leading to death	0	(0)	0	(0)	0	(0)
Serious adverse events not leading to death	1	(0.3)	0	(0)	1	(0.2)
Discontinuations of study treatment due to adverse events	3	(0.9)	0	(0)	3	(0.7)
Drug related adverse events [b]	7	(2.1)	1	(0.9)	8	(1.8)
Other significant adverse events	0	(0)	0	(0)	0	(0)
	Total number of adverse events					
Adverse events	26		12		38	

Table S 6 Number (%) of subjects who had at least 1 adverse event in any category, and total numbers of adverse events (safety analysis set)

Category of adverse event	N (%) of subjects who had an adverse event in each category[a]		
	Esomprazole (N=337)	Omeprazole (109)	Total (N=446)
Serious adverse events	1	0	1
Drug related adverse events [b]	10	3	13

[a] Subjects with multiple events in the same category are counted only once in that category. Subjects with events in more than 1 category are counted once in each of those categories.

[b] Drug related AEs are those for which there was a possible relationship to investigational product as judged by the investigator

Table S 7 Number (%) of subjects with the most commonly reported[a] adverse events, sorted by decreasing order of frequency as summarised over all treatment groups (safety analysis set)

Adverse event (preferred term)	Number (%) of subjects who had an adverse event		
	Esomprazole (N=337	Omeprazole (N=109)	Total (N=446)
Pyrexia	4 (1.2)	4 (3.7)	8 (1.8)

[a] Events with a total frequency of ≥1% across all treatment groups are included in this table.

Overall both drugs were well tolerated. A similar low frequency and intensity of adverse events were reported in both treatment groups. The most common adverse event was pyrexia with 1.2% in Esomeprazole group and 3.7 % in Omeprazole group, Most of Pyrexia are with mild or moderate degree. 1 serious adverse event was reported (cerebrovascular disorder) in Esomeprazole group and was not considered drug related by the investigator. There was no mortality in the study. Safety data from this study did not suggest any difference in the safety profile of the two study drugs. Safety findings were evenly distributed across the treatment groups.

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