Clinical Study Report Synopsis

Drug Substance	Esomeprazole
Study Code	NIS-GCN-DUM-2010/1
Edition Number	Version 3.1
Date	23 March 2012

A Survey on Peptic Ulcer Bleeding in China

Study dates: First Patient enrolled: 18 October 2010
Last patient last visit: 30 July 2011

Phase of development: Non-interventional study

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

Study centre(s)

Fifty two qualified sites in China participated in this study.

Publications

None at the time of writing this report.

Objectives and criteria for evaluation

Table S1 Primary and secondary objectives and outcome variables

Objectives	Outcome variables
Primary To investigate the proportion of high-risk (Forrest Ia-IIb) patients in patients with peptic ulcer bleeding (PUB).	**Primary** Proportion High-risk Patients with PUB.
Secondary **1.** To evaluate the proportion of patients who received endoscopic treatment among patients with high-risk (Forrest Ia-IIb) PUB. **2.** To evaluate the types of endoscopic treatment that the patients with high-risk (Forrest Ia-IIb) PUB received. **3.** To evaluate the success rate of endoscopic treatment among patients with PUB who received endoscopic treatment (Success was defined as no visible bleeding after endoscopic treatment).	**Secondary** **1.** Treatment proportion on topical drug injection, heat hemostasis and mechanical hemostasis, among high-risk PUB patients with endoscopic treatment at V1. **2.** Re-bleeding rate of high risk patients for Days 1-3, Days 4-5 and Days 6-30, respectively, after successful endoscopic treatment. **3.** Successful treatment rate on high-risk patients with endoscopic treatment.

Objectives	Outcome variables
Secondary	
4. To evaluate the clinically significant re-bleeding rates with or without PPIs or H2RA treatment at Days 3, 5 and 30 after successful endoscopic treatment among patients with high-risk (Forrest Ia-IIb) PUB (Re-bleeding was defined as recurrence of hematemesis and/or melena, or complicating shock or decrease in haemoglobin level by at least 20g/L).	
5. To evaluate the rates of endoscopic re-treatment at Days 3, 5 and 30 after successful endoscopic treatment among patients with high-risk (Forrest Ia-IIb) PUB.	
6. To evaluate the surgery rates at Days 3, 5 and 30 after endoscopy in all patients with PUB, in patients with high-risk (Forrest Ia-IIb) PUB, and in patients with high-risk (Forrest Ia-IIb) PUB who received successful endoscopic treatment.	

Study design

This was a multicentre, prospective and observational study collecting the clinical data regarding the treatment status of Chinese patients with PUB.

Target subject population and sample size

The study aimed to include 1000 patients with PUB. Assuming a proportion of high-risk patients of 20% in patients with PUB, the 95% confidence interval for the proportion of high-risk patients would be ±2.5% for the 1000 patients.

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

Not applicable due to the non-interventional nature of the study.

Duration of treatment

NA

Statistical methods

Descriptive statistics were used for each variable as this was a non-interventional study. Therefore no hypothesis test was used and there was no need to define a significance level. For quantitative variables, descriptive statistics including patient number, mean, standard deviation, median, minimum and maximum were listed. Categorical data were presented by the number and percentage of patients in each category. Unless otherwise specified, all percentages were based on non-missing data.

Subject population

A total of 1040 subjects were enrolled at 52 sites in China, including 993 (95.5%) who completed the study and 47 (4.5%) who prematurely discontinued the study. One thousand and six subjects were included in the FAS and 34 (3.4%) were excluded from the FAS.

Table S 2 Summary Table of Statistical Analysis Set

	N (%)
Total N enrolled	1040
FAS	1006
N exluded from FAS	34(3.4%)
Discontinuations due to participation in another clinical study	1(0.1%)
Discontinuations due to age lower than 18 years	8(0.8%)
Discontinuations due to failure of of marked upper GI bleeding symptoms	8(0.8%)
Discontinuations due to failure of endoscopically confirmed PUB	2(0.2%)
Inconsistency of the study indication	16(1.6%)
Screen failure	1(0.1%)

Note：The number of FAS is used as the denominator for percentages.
One subject may be removed for one or more reasons Inclusion criterion: 2. Equal or more than 18 years of age；3. Presence of marked upper GI bleeding symptoms； 4.endoscopically confirmed PUB (Forrest I-III)。Exclusion criterion: 1. Participation in other clinical study.

1006 subjects were included in the FAS. 34 (3.4%) were excluded from the FAS for the reasons of inconsistency with the study indication (16, 1.6%), lower than 18 years of age (8, 0.8%), absence of marked upper GI bleeding symptoms (8, 0.8%), non-endoscopically confirmed PUB (2, 0.2%), participation in other clinical study (1, 0.1%), and screen failure (1, 0.1%).

Table S 3 Subjects Demographics

Parameter		*N (%)* FAS (N=1006)
Age (years)	Number(missing number)	1006(0)
	Mean(SD)	50.97(16.705)
	Median	53.0
	Minimum-maximum	18.0～88.0
Gender	Male	792(78.7%)
	Female	214(21.3%)
	Total	1006(100.0%)
Race	Caucasian	0
	Black	0
	Asian	1006(100.0%)
	Other	0
	Total	1006(100.0%)

Note：Date of birth for [E0064016] was treated as 1940-06-15 as day and month were unknown.
Age (years) = (date of informed consent-date of birth/365.25) and rounded to one decimal.

In the FAS, the average age of subjects was 50.97 years (18.0～88.0 years); there were 792(78.7%) males and 214 (21.3%) females; all of the 1006 patients were of Asian origin. The subject demographics are detailed in Table S3.

Table S 4 Baseline Clinical Symptoms of GI Bleeding

Index		*N (%) FAS (N=1006)*
Time from GI bleeding to enrolment (days)	Number(missing number)	1006(0)
	Mean(SD)	12.16(124.62)
	Median	4.0
	Minimum-maximum	0.0～3723.0 *
Cumulative duration of symptoms of GI bleeding (hours)	Number(missing number)	999(7)
	Mean(SD)	91.10(124.79)
	Median	51.0
	Minimum-maximum	0.1～1464.0 *

Note：Time from GI bleeding to enrolment = date of informed consent - date of start of GI symptom
* All the data values in questions have been checked and verified to the best of our knowledge at the time of writing this CSR.

In the FAS, the mean and median times from GI bleeding enrolment were 12.16 days and 4.0 days respectively with a range of 0 to 3723 days. The gap between the mean and the median was caused by some extreame data values which have been accounted for and thus the median here presents a more accurate summary. The mean and median cumulative duration of GI bleeding symptoms was 91.1 hours and 51.0 hours respectively with a range of 0.1 to 1464 hours. The details are provided in Table S4.

Table S 5 Summary of Key Baseline Characteristics

Index	*Category*	*FAS* *N (%)* *(N=1006)*	*Non-High-risk PUB* *N (%)* *(N=569)*	*High-risk PUB not treated by endoscopy* *N (%)* *(N=327)*	*High-risk PUB not treated by endoscopy* *N (%)* *(N=110)*
Time from symptom to endoscopy	⩽ 1 day	192 (19.1%)	60 (10.5%)	87(26.6%)	45 (40.9%)
	⩽ 2 days	349 (34.7%)	152 (26.7%)	139 (42.5%)	58 (52.7%)
	⩽ 3 days	498 (49.5%)	234 (41.1%)	190 (58.1%)	74 (67.3%)
	⩽ 4 days	635 (63.1%)	322 (56.6%)	221 (67.6%)	92 (83.6%)
	⩽ 5 days	709 (70.5%)	370 (65.0%)	243 (74.3%)	96 (87.3%)
	> 6 days	296 (29.4%)	198 (34.8%)	84 (25.7%)	14 (12.7%)
Age group	⩾50 years	557 (55.4%)	331 (58.2%)	174 (53.2%)	52 (47.3%)
	⩾60 years	339 (33.7%)	203 (35.7%)	101 (30.9%)	35 (31.8%)
	⩾65 years	238 (23.7%)	144 (25.3%)	69 (21.1%)	25 (22.7%)
Previous helicobacter pylori infection	Yes	30 (3.0%)	15 (2.6%)	11 (3.4%)	4 (3.6%)
	No	53 (5.3%)	30 (5.3%)	17 (5.2%)	6 (5.5%)
	Unknown	224 (22.3%)	133 (23.4%)	62 (19.0%)	29 (26.4%)
	Not done	92 (9.1%)	50 (8.8%)	31 (9.5%)	11 (10.0%)
Forrest grading	Forrest Ia	3 (0.3%)	0 (0.0%)	1 (0.3%)	2 (1.8%)
	Forrest Ib	129 (12.8%)	0 (0.0%)	74 (22.6%)	55 (50.0%)
	Forrest IIa	159 (15.8%)	0 (0.0%)	113 (34.6%)	46 (41.8%)
	Forrest IIb	146 (14.5%)	0 (0.0%)	139 (42.5%)	7 (6.4%)
	Forrest IIc	41 (4.1%)	41 (7.2%)	0 (0.0%)	0 (0.0%)
	Forrest III	475 (47.2%)	475 (83.5%)	0 (0.0%)	0 (0.0%)
	Unevaluable	14 (1.4%)	14 (2.5%)	0 (0.0%)	0 (0.0%)
Systemic symptom due to bleeding	Syncope	184 (18.3%)	107 (18.8%)	55 (16.8%)	22 (20.0%)
	Shock	51 (5.1%)	21 (3.7%)	22 (6.7%)	8 (7.3%)
	Tachycardia or hypotension	53 (5.3%)	22 (3.9%)	23 (7.0%)	8 (7.3%)

Table S 6 Proportion High-risk (Forrest Ia-IIb) Patients with PUB

Index	*FAS(N=1006)*	
	n(%)	*95%CI*
Patients with PUB	1006(100.0%)	99.6%-100.0%
Patients with high-risk PUB	437(43.4%)	40.3%-46.6%
Forrest Ia	3(0.7%)	0.1%-2.0%
Forrest Ib	129(29.5%)	25.3%-34.0%
Forrest IIa	159(36.4%)	31.9%-41.1%
Forrest IIb	146(33.4%)	29.0%-38.0%

Notes：Patients with PUB：endoscopically confirmed PUB (Forrest I-III)；Patients with high-risk PUB： PUB with Forrest grade Ia to IIb upon endoscopy

Forrest grading includes gastric ulcer bleeding grading and duodenal ulcer bleeding grading. The worst Forrest grade was used if a patient had both grades.

In the FAS, 437 patients were noted to have high-risk PUB, contributing to the high-risk PUB rate (95%CI) of 43.4% (40.3%, 46.6%). The proportions of Forrest Ia, Forrest Ib, Forrest IIa, Forrest IIb PUB were 0.7%, 29.5%, 36.4%, and 33.4%, respectively. The details are provided in Table S6.

Table S 7 Endoscopic Treatment Status in Patients with High-risk PUB

Index	*FAS(N=1006)*	
	n(%)	*95%CI*
Patients with high-risk PUB who received endoscopic treatment at V1	110(25.2%)	21.2%-29.5%
topical drug injection	87(79.1%)	70.3%-86.3%
heat hemostasis	8(7.3%)	3.2%-13.8%
mechanical hemostasis	64(58.2%)	48.4%-67.5%
Patients with high-risk PUB who received endoscopic treatment at V1	110(25.2%)	21.2%-29.5%
Forrest Ia	2(1.8%)	0.2%-6.4%
Forrest Ib	55(50.0%)	40.3%-59.7%
Forrest IIa	46(41.8%)	32.5%-51.6%
Forrest IIb	7(6.4%)	2.6%-12.7%
Day 3 after successful endoscopic treatment		
Re-bleeding	12(11.0%)	5.8%-18.4%
Day 5 after successful endoscopic treatment		
Re-bleeding	4(3.7%)	1.0%-9.1%
Day 30 after successful endoscopic treatment		
Re-bleeding	1(0.9%)	0.0%-5.0%

Table S 8 PUB Disease Status after Endoscopic Treatment

Index	FAS(N=1006)	
	n(%)	95%CI
Patients with PUB	1006(100.0%)	99.6%-100.0%
First 3 days following endoscopy		
Surgery	6(0.6%)	0.2%-1.3%
Death	0	0.0%-0.4%
First 5 days following endoscopy		
Surgery	7(0.7%)	0.3%-1.4%
Death	0	0.0%-0.4%
First 30 days following endoscopy		
Surgery	15(1.5%)	0.8%-2.4%
Death	2(0.2%)	0.0%-0.7%
Patients with high-risk PUB	437(43.4%)	40.3%-46.6%
First 3 days following endoscopy		
Surgery	4(0.9%)	0.2%-2.3%
Death	0	0.0%-0.8%
First 5 days following endoscopy		
Surgery	4(0.9%)	0.2%-2.3%
Death	0	0.0%-0.8%
First 30 days following endoscopy		
Surgery	8(1.8%)	0.8%-3.6%
Death	2(0.5%)	0.1%-1.6%
High-risk PUB successfully treated by endoscopy	109(99.1%)	95.0%-100.0%
First 3 days following endoscopy		
Surgery	2(1.8%)	0.2%-6.5%
Death	0	0.0%-3.3%
First 5 days following endoscopy		
Surgery	2(1.8%)	0.2%-6.5%
Death	0	0.0%-3.3%
First 30 days following endoscopy		
Surgery	2(1.8%)	0.2%-6.5%
Death	0	0.0%-3.3%

Among the patients with high-risk PUB, 110 (25.2%) received endoscopic treatment at Visit 1. Among the 110 patients who received endoscopic treatment; 87 (79.1%) received topical drug injection; 8 (7.3%) received heat hemostasis; and 64 (58.2%) received mechanical hemostasis. The endoscopic treatment was successful in 109 (99.1%) of the 110 patients.

Re-bleeding was noted in 12 (11.0%), 4 (3.7%), and 1 (0.9%) patients for Days 1-3, Days 4-5 and Days 6-30, respectively, after successful endoscopic treatment.

The details for patients with high-risk PUB and endoscopic treatment status after endoscopic treatment are provided in Tables S7 and S8.

Summary of efficacy results

NA

Summary of pharmacokinetic results

NA

Summary of pharmacodynamic results

NA

Summary of pharmacokinetic/pharmacodynamic relationships

NA

Summary of pharmacogenetic results

NA

Summary of safety results

As there was no safety objective, AE was not collected in a solicited manner.

Two (0.2%) deaths occurred during the study. One death case was due to uncontrolled bleeding; the patient received endoscopy therapy and multiple medications incl. an AZ product, Losec injection, developed “uncontrolled ulcer bleeding”, and died of complicated hemorrhagic shock. The other case died for “other reason” (multiple basic diseases, financial insufficiency, insufficient in-hospital treatment, complicated by old age and generalized organ failures).