Clinical Study Protocol

Drug Substance	Esomeprazole
Study Code	D961DC00007
Edition Number	1.0
Date	

A multi-center, randomised, double-blind, parallel-group phase III study to assess high dose esomeprazole i.v. treatment (bolus infusion of 80 mg followed by a continuous infusion of 8 mg per hour administered for 72 hours) for prevention of rebleeding in patients in China with primary successful endoscopic haemostatic therapy of a bleeding peptic ulcer, with cimetidine as active control

Sponsor:

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The following Amendment(s) and Administrative Changes have been made to this protocol since the date of preparation:

Amendment No.	Date of Amendment	Local Amendment No:	Date of Local Amendment

Administrative Change No.	Date of Administrative Change	Local Administrative Change No.	Date of Local Administrative Change

AstraZeneca

PROTOCOL SYNOPSIS

A multi-center, randomised, double-blind, parallel-group phase III study to assess high dose esomeprazole i.v. treatment (bolus infusion of 80 mg followed by a continuous infusion of 8 mg per hour administered for 72 hours) for prevention of rebleeding in patients in China with primary successful endoscopic haemostatic therapy of a bleeding peptic ulcer, with cimetidine as active control

National Principal Investigator

Study centre(s) and number of patients planned

The plan is to randomise 200 evaluable patients with successful endoscopic haemostasis of peptic ulcer bleeding (PUB) into the study. To reach this number of randomised patients, at least 600 patients with upper gastrointestinal bleeding will be enrolled in approximately 20 centres in China. The proposed number of randomised patients per centre is 10.

Study period	Phase of development
Estimated date of first patient enrolled	III
Estimated date of last patient completed	

Objectives

Primary objective

The primary objective is to describe the rate of clinically significant rebleeding during 72 hours continuous i.v. infusion of high dose esomeprazole in patients in China with primary successful endoscopic haemostatic therapy of a bleeding peptic ulcer, with cimetidine as active control.

Secondary objectives

The secondary objectives are to, in patients in China with primary successful endoscopic haemostatic therapy of a bleeding peptic ulcer, describe the outcome after 72 hours continuous i.v. infusion of high dose esomeprazole, with cimetidine as active control, with regard to the following (where the time period begins at start of i.v treatment):

- The rate of clinically significant rebleeding within 7 days and 30 days.
- The proportion of patients who within 72 hours and 30 days, had endoscopic re-treatment due to rebleeding.
- The proportion of patients who, within 72 hours and 30 days, had surgery (except endoscopic treatment) due to rebleeding.
- The number of blood units transfused within 72 hours and 30 days.

Safety objectives

To assess the safety and tolerability of 72 hours continuous i.v. infusion of high dose esomeprazole in patients in China with peptic ulcer bleed.

To assess the safety and tolerability of open oral treatment with esomeprazole 40 mg once daily for 27 days, following 72 hours continuous i.v. infusion of high dose esomeprazole or cimetidine.

Study design

This will be a Chinese multi-center, randomised, double-blind, parallel-group study in patients who have undergone successful primary endoscopic haemostasis of a bleeding peptic ulcer assessing the rate of clinically significant rebleeding and safety during 72 hours of continuous i.v. infusion of esomeprazole, with continuous i.v infusion of cimetidine as active control. After the i.v infusion treatments, all patients will receive active treatment with 40 mg oral esomeprazole for 27 days.

Target patient population

Male and female patients, 18-70 years who have undergone successful endoscopic haemostatic treatment of a bleeding gastric or duodenal peptic ulcer.

Investigational product (IP), dosage and mode of administration

Esomeprazole powder for solution for infusion 40 mg will be used for the i.v. administration.

Esomeprazole i.v.	Given as 80 mg bolus infusion during 30 min
Esomeprazole i.v.	8 mg/h constant infusion during 71.5 hours

Esomeprazole tablets 40 mg will be used for the oral treatment phase. All patients will receive oral 40 mg esomeprazole tablets once daily during 27 days after the initial i.v. treatment.

Comparator, dosage and mode of administration

Cimetidine solution for infusion 200 mg will be used for the i.v. administration.

Cimetidine i.v.	Given as 200 mg bolus infusion during 30 min
Cimetidine i.v.	60 mg/h constant infusion during 71.5 hours

Esomeprazole tablets 40 mg will be used for the oral treatment phase. All patients will receive oral 40 mg esomeprazole tablets once daily during 27 days after the initial i.v. treatment.

Duration of treatment

The i.v. treatment phase is 72 hours and is followed by 27 days of open oral treatment phase.

Outcome variable(s)

Efficacy

Primary outcome variable:

- Clinically significant rebleeding within 72 hours of continuous infusion of esomeprazole or cimetidine.

Secondary variables:

- Clinically significant rebleeding within 7 days and 30 days.
- Requirement for endoscopic re-treatment within 72 hours and 30 days.
- Requirement for surgery within 72 hours and 30 days.
- Number of blood units transfused within 72 hours and 30 days.

Patient reported outcomes (Not applicable)

Health economics (Not applicable)

Pharmacokinetic (Not applicable)

Pharmacodynamic (Not applicable)

Safety

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

Statistical methods

The primary objective in the study will be to describe the rate of clinically significant rebleeding during 72 hours continuous i.v. infusion of high dose esomeprazole after primary successful endoscopic haemostatic therapy, with the number of clinically significant rebleedings at 7 and 30 days as secondary objectives which correspond to those used in the global PUB study. Since the global study did not have any patients from China, and this study is not sufficiently powered to show differences between the two treatments, the aim is to assess whether the outcomes in China are in line with the results in the global PUB study. Therefore, the results will be displayed using descriptive statistics without any formal statistical hypothesis testing.

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

The following abbreviations and special terms are used in this study Clinical Study Protocol.

Abbreviation or special term	Explanation
AE(s)	Adverse event(s) (see definition in Section 6.4.1)
ALT	Alanine Aminotransferase
ALP	Alkaline Phosphatase
APTT	Activated Partial Thromboplastin Time
ASA	Acetyl Salicylic Acid
ASA class	American Society of Anaesthesiologist's physical status classification
AST	Aspartate Aminotransferase
BP	Blood pressure
CNS	Central nervous system
COX-2	Cyclooxygenase 2
CSA	Clinical Study Agreement
CSP	Clinical Study Protocol
CSR	Clinical Study Report
DAE	Discontinuation of Investigational Product due to adverse event
DMC	Data Management Centre
DMP	Data Management Plan
E-code	Enrolment code
EC	Ethics Committee
ECG	Electrocardiogram
eCRF	Electronic case report form
(e)GFR	(estimated) Glomerular filtration rate
GERD	Gastroesophageal Reflux Disease
GI	Gastrointestinal
eg	Example gratia
FAS	Full Analysis Set
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GMP	Good Manufacturing Practice

Abbreviation or special term	Explanation
h	Hour
H. pylori	Helicobacter pylori
H2RA	Histamine type 2-Receptor antagonist
Haematemesis	The vomiting of blood
Haematochezia	The passage of bright, red blood in stools with a volume large enough to indicate it comes from upper GI-tract
Hct	Haematocrit
Hb	Haemoglobin
IB	Investigator's Brochure
ICF	Informed Consent Form
IP(s)	Investigational Product(s)
i.v.	Intravenous
ICH	International Conference on Harmonisation
INR	International Normalized Ratio
IVRS	Interactive Voice Response System
IWRS	Interactive Web Response System
MedDRA	Medical Dictionary for Regulatory Activities
mg	Milligram
min	Minute
ml	Milliliter
mm	Millimeter
MDRD	Modification of Diet in Renal Disease
NB	Nota bene
NSAID(s)	Non-Steroidal Anti-Inflammatory Drug(s)
OAE	Other Significant Adverse Event
PPI(s)	Proton Pump Inhibitor(s)
PI	Principal investigator
PTC	Prothrombin complex
PUB	Peptic Ulcer Bleeding
SAE	Serious Adverse Event (see definition in Section 6.4.2)
SUSARs	Suspected Unexpected Serious Adverse Reactions
ULN	Upper Limit of Normal

Abbreviation or special term	Explanation
WBC	White Blood Cell Count
WBDC	Web Based Data Capture
WHO	World Health Organisation

1. INTRODUCTION

1.1 Background

Peptic ulcer bleeding (PUB) is the main cause of non variceal upper gastrointestinal bleeding, which is associated with considerable morbidity and mortality with reported incidence ranging from 48 to 160 cases per 100 000 adults per year (Barkun et al 2010). Although the incidence of peptic ulcers has decreased substantially over the last decades, PUB has not and mortality remains an issue with reported rates at 5 to 14% in population based epidemiological studies, and pooled rates of approximately 4% in recent interventional clinical trials with PPIs (Blatchford et al 1997, van Leerdam et al 2003, Leontiadis et al 2006, Barkun et al 2010). Hence, the mortality rate within 30 days in these patients is approximately 5-10%. These figures are remarkably unchanged during the last 30 years in spite of the introduction of more effective drugs in ulcer treatment such as Histamine type 2-Receptor Antagonists (H2RA) and Proton Pump Inhibitors (PPIs) in this period of time. Partial explanations to this apparent paradox are the increased use of Non-Steroidal Anti-Inflammatory Drugs (NSAIDs) and the increasing mean age of the population in the same time period. The risk of mortality depends on age, the presence or absence of comorbidities, the severity of the actual bleeding, and the occurrence of rebleeding (Holster and Kuipers 2011). Endoscopic haemostatic therapy is the cornerstone in treatment of high risk PUB patients. Despite this treatment rebleeding occurs in about 10 to 20% of the cases during the first month after the initial bleeding episode (Leontiadis et al 2006). Rebleeding has been reported to increase the risk for morbidity and fatal outcome, the need for repeated endoscopic treatment and surgery and to prolonged hospitalisation, particularly in patients with significant comorbidity (Rockall et al 1996, Kupfer et al 2000,van Leerdam et al 2003).

Peptic ulcers in the stomach and in the duodenum occur in patients where the normal resistance to hydrochloric acid secreted into the stomach is reduced e.g. by *Helicobacter pylori* (*H. pylori*) infection or by the action of NSAID medication. PUB is the result of erosion by acid and peptic enzymes of a blood vessel in the submucosa or the muscularis mucosae in relation to the development of peptic ulcer (Speechler 2002, Schiller et al 2002, Spiro 1993), and it is characterized by clinical symptoms such as haematemesis, melaena, or haematochezia (please see List of Abbreviations and Definitions of Terms). Severe blood loss may lead to shock and circulatory collapse, and PUB therefore represents a medical emergency. A factor contributing to prolonged bleeding is the fact that the acidic environment in the stomach impairs normal haemostatic mechanisms and is thus contributing to prolonged bleeding (Green et al 1978, Patchett et al 1989). Pharmacological inhibition of acid secretion would therefore act to favour haemostasis and thereby to reduce the risk for rebleeding (Li et al 2000).

Initial management aims at resuscitation and stabilisation of circulation and vital functions, and a diagnostic upper gastrointestinal (GI) endoscopy should be undertaken early (within 24 hours) (Sung et al 2011). The aim of the endoscopy is to characterise the source of bleeding, including stigmata of recent haemorrhage, and also to treat the bleeding ulcer endoscopically,

if indicated and possible. If the bleeding cannot be controlled endoscopically, urgent surgery or arterial coiling/angiographic embolisation is necessary (Sung et al 2011).

According to the current consensus early stratification into low- and high-risk categories for rebleeding and mortality is recommended based on risk scores that usually include age, presence of shock, co-morbid conditions, diagnosis and endoscopic stigmata of recent haemorrhage or so called endoscopic stigmata (Forrest classification) (Barkun et al 2010).

During endoscopy one of the following stigmata is observed (Lau et al 1998):

Forrest Ia – arterial bleeding
Forrest Ib – oozing bleeding
Forrest IIa – non-bleeding visible vessel
Forrest IIb – adherent clot
Forrest IIc – flat pigmented spot
Forrest III – clean ulcer base

Endoscopic predictors of increased risk for rebleeding and mortality include active bleeding (especially arterial bleeding rather than oozing), non-bleeding visible vessel or adherent clot, ulcer size (generally >2 cm), ulcer location (posterior lesser gastric curvature or posterior duodenal wall) (Barkun et al 2010). Those with high risk stigmata (Forrest Ia- IIb) should receive endoscopic treatment – the cornerstone of treatment in these cases, to stop ongoing bleeding and prevent rebleeding (Forrest et al 1974, Laine and Peterson 1994, Lau et al 1998), while endoscopic treatment is not necessary for patients with low risk endoscopic stigmata (Forrest IIc and III). In case of Forrest IIb, the usual recommendation is to attempt to remove the clot and decide on the necessity of endoscopic treatment when seeing the ulcer base. For an adherent clot (Forrest IIb) resistant to irrigation, endoscopy treatment (injection treatment combined with either thermal coagulation or mechanical device) could be considered as in this situation a true high-risk and low-risk stigmata cannot be differentiated (Sung et al 2011).

Based on earlier published studies showing a beneficial effect of treatment with PPIs in further reducing rebleeding rate (Hasselgren et al 1997, Schaffalitzky de Muckadell et al 1997, Khuroo et al 1997, Laine et al 2010), off-label use of PPIs (often in higher doses than commonly used in other indications) have gained acceptance. Some of the most compelling clinical studies showing an effect of PPIs in this indication were performed in Asian populations (Khuroo et al 1997, Lau et al 2000, Leontiadis et al 2005). Due to differences in drug metabolism between races doubts were raised as to whether results from such studies were totally applicable to Western populations. Therefore, a global placebo controlled PUB study (Sung et al 2009) with high dose esomeprazole i.v. dose regimen (80 mg bolus followed by 8 mg/hour during 72 hours) for prevention of rebleeding after successful endoscopic haemostasis was performed in high risk patients (Forrest Ia-IIb). This study showed a significant reduction of high dose esomeprazole regimen compared to placebo on the primary outcome rebleeding rate at 72 hours after endoscopic treatment (5.9% vs 10.3%). High dose esomeprazole i.v. regimen is the only pharmacological treatment that has met regulatory requirements for approval of the indication prevention of rebleeding and is currently approved in more than 100 countries worldwide, however, not in China.

Esomeprazole is the first PPI developed as an enantiomer. It has been shown to be effective in suppressing gastric acid production and is approved for acid related disorders such as Gastroesophageal Reflux Disease (GERD) and PUB (Miner et al 2003, Miner et al 2006, Röhss et al 2004).

1.2 Research hypothesis

The hypothesis in this study is that the rate of clinically significant rebleeding within 72 hours after start of high dose esomeprazole i.v. treatment in China will be in line with the result in the global PUB study and that the esomeprazole i.v. infusion is safe and well tolerated. However, formal statistical testing is not part of this study due to the small sample size and the expected small number of rebleeding events.

1.3 Rationale for conducting this study

Low-dose esomeprazole i.v. regimen (40 mg bid) for treatment of patients with PUB (Forrest IIc-III) has been approved in China. This study aims to fulfill the post-approval commitment to perform a clinical study to explore high dose esomeprazole i.v. regimen (80 mg + 8 mg/h) in prevention of rebleeding in high risk PUB patients (Forrest Ia-IIb) in China.

The PUB project with esomeprazole i.v. in China was started in 2005. A non-inferiority clinical study comparing the low dose esomeprazole i.v. regimen (40 mg bid) to omeprazole i.v. 40 mg bid (AZ study D961DL00004) was started 2006 in patients presenting with bleeding peptic ulcer (Forrest grade I-III), in accordance with approved indication and PPI-dose in China.This study was completed in February 2008, almost at the same time point as the global PUB study was completed in March 2008. The Chinese regulatory submission aimed at getting approval of treating patients with PUB (Forrest grade I-III) with esomeprazole 40 mg bid. However, in June, 2010, low dose esomeprazole i.v. regimen was granted approval in China “to be used in low-risk patients with acute gastric or duodenal ulcers bleeding (Forrest grade IIc-III by endoscopy) when the oral route is not applicable”. The indication is not related to the prevention of rebleeding, but rather treatment of PUB.

The condition for approval of the low dose esomeprazole i.v. regimen in China for treatment of PUB (Forrest IIc-III) was expressed “the applicant needs to continue the clinical study in China, and explore the reasonable usage and dosage to guide clinical treatment for the prevention of rebleeding following therapeutic endoscopy for acute non-variceal upper GI bleeding (high-risk patients)” by performing a similar study as the global PUB study.

Given the conclusive results of the global PUB study, AZ did not agree to perform another placebo-controlled study, based on ethical considerations. However, in order to evaluate the feasibility to perform a superiority study with an active comparator in China, information was needed about the proportion of patients at high risk for rebleeding (Forrest Ia-IIb) receiving endoscopic therapy and whether the rebleeding rate of high risk patients is lower or higher or similar as compared to that in Western countries and to what extent the different endoscopic techniques are applied by Chinese physicians as the first choice of endoscopic treatment. To meet this need, A Survey on PUB in China (AZ study NIS-GCN-DUM- 2010/1) was

conducted between October 2010 and July 2011. This observational study embraced a full analysis set (FAS) of 1006 patients recruited at 52 centres. Of these 437 (43%) were classified as high risk for rebleeding (Forrest class Ia-IIb; only 1.8% with Forrest Ia) and 110/437 (25%) of the high risk patients received endoscopic treatment. The treatment modalities used among those receiving endoscopic haemostasis were topical drug injection (79.1%), thermal hemostasis (7.3%) and mechanical haemostasis (58.2%).

The China PUB Survey showed that currently in China there seem to be limited access to centers with sufficient number of high risk patients routinely receiving endoscopic treatment. Only 8 of the 52 sites had >2 patients with endoscopic treatment and in only 5 of the 52 sites ≥50% of high risk patients received endoscopic treatment. In addition, no clear pattern of rebleeding difference at 72 hours was observed between those receiving vs. those not receiving endoscopic treatment (11% vs 10.4%) and there was an unexpected high re-bleeding rate in low-risk patients (Forrest IIc-III; 5.1%).

The non interventional PUB survey indicated that it is currently not feasible in China to do a large superiority study in the indication prevention of rebleeding in high risk PUB patients (Forrest Ia-IIb). However, in order to fulfill the post-approval commitment for the approval of low-dose esomeprazole i.v. regimen, this study will explore and provide descriptive data on the use of high dose esomeprazole i.v. regimen in Chinese high risk patients (Forrest Ia-IIb) for prevention of rebleeding after succesful endoscopic haemostatic therapy, without statistical inference and with cimetidine as active control (see Section 3.2). Assessment of safety and tolerability of high dose esomeprazole i.v treatment in patients in China will be an important objective in the study. The primary objective in the study will be to describe the rate of clinically significant rebleeding during 72 hours continuous i.v. infusion of high dose esomeprazole after primary successful endoscopic haemostatic therapy, with the number of clinically significant rebleedings at 7 and 30 days as secondary objectives. Other secondary objectives aimed to reflect the consequences of rebleeding are the number of patients who had endoscopic re-treatment or surgery within 72 hours and 30 days due to rebleeding, and the number of transfused blood units within 72 hours and 30 days. These objectives all correspond to those used in the global PUB study, and it could thus be possible to assess whether the outcomes in China show a similar pattern as in the global PUB study.

1.4 Benefit/risk and ethical assessment

An overall risk benefit assessment of esomeprazole is presented in the Investigator's Brochure (IB) for Esomeprazole i.v. (Edition no. 8, 2012). The margins of safety for maximal as well as steady-state plasma concentrations of esomeprazole in animals versus man are reassuring. A bolus infusion of 80 mg during 30 minutes followed by continuous infusion of 8 mg/h of esomeprazole has been well tolerated in the global PUB study, including both Asian and Western patient population. Thus, the potential risks related to drug exposure in the current study is limited. Risks associated with study related procedures are also limited, as study participation for the individual patient includes routine management and, driven by study participation, careful monitoring and follow-up of the disease under study during the hospitalisation and after discharge from hospital.

The choice of cimetidine as active control, rather than placebo, during the first 72 hours in this study is being discussed in Section 3.2. Cimetidine has the indication treatment of peptic duodenal or gastric ulcer and is considered safe to use in this patient population in combination with endoscopic haemostatic therapy with regard to ethical standards. Any patient developing signs of a rebleeding will be immediately investigated and treated.

The risk benefit assessment for this study is deemed favourable, as each patient will receive endoscopic treatment for a peptic ulcer, currently considered the cornerstone of treatment in patients with PUB Forrest Ia-IIb (Sung et al 2011, Holster and Kuipers 2011, Laine 2012) and subsequent acid suppression as adjunct treatment. In addition each patient will be carefully monitored and treated to ensure ulcer healing. The benefits for each patient in participating in the study should therefore be greater than potential risks.

2. STUDY OBJECTIVE

2.1 Primary objective

The primary objective is to describe the rate of clinically significant rebleeding during 72 hours continuous i.v. infusion of high dose esomeprazole in patients in China with primary successful endoscopic haemostatic therapy of a bleeding peptic ulcer, with cimetidine as active control.

2.2 Secondary objectives

The secondary objectives are to, in patients in China with primary successful endoscopic haemostatic therapy of a bleeding peptic ulcer, describe the outcome after 72 hours continuous i.v. infusion of high dose esomeprazole, with cimetidine as active control, with regard to the following (where the time period begins at start of i.v treatment):

- The rate of clinically significant rebleeding within 7 days and 30 days.
- The proportion of patients who within 72 hours and 30 days, had endoscopic re-treatment due to rebleeding.
- The proportion of patients who, within 72 hours and 30 days, had surgery (except endoscopic treatment) due to rebleeding.
- The number of blood units transfused within 72 hours and 30 days.

2.3 Safety objectives

To assess the safety and tolerability of 72 hours continuous i.v. infusion of high dose esomeprazole in patients in China with peptic ulcer bleed.

To assess the safety and tolerability of open oral treatment with esomeprazole 40 mg once daily for 27 days, following 72 hours continuous i.v. infusion of high dose esomeprazole or cimetidine.

3. STUDY PLAN AND PROCEDURES

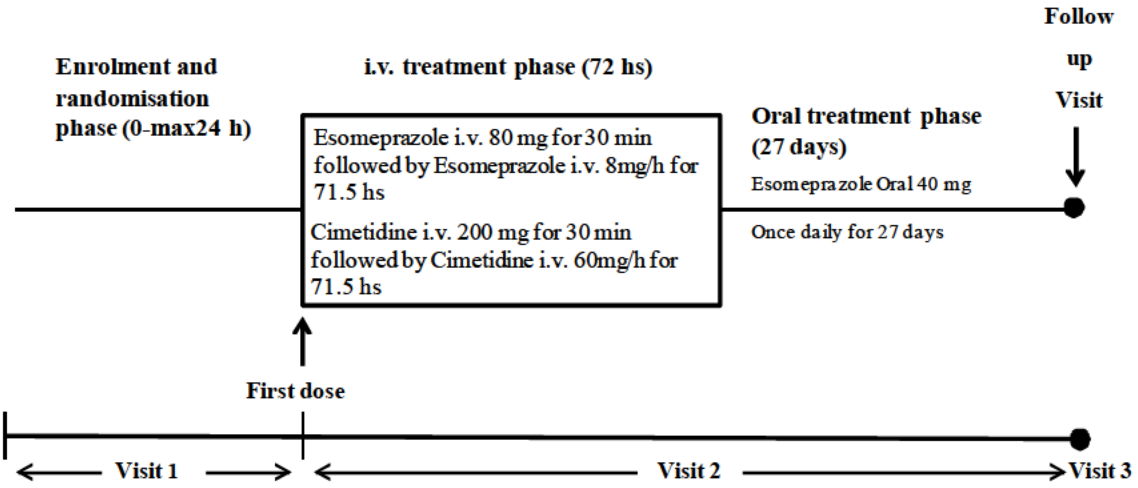
This Clinical Study Protocol (CSP) has been subject to a peer review according to AstraZeneca standard procedures.

3.1 Overall study design and flow chart

This will be a multi-center, randomised, double-blind, parallel-group study in patients who have undergone successful primary endoscopic haemostasis of a bleeding peptic ulcer. The primary outcome variable will be clinically significant rebleeding within 72 hours of continuous i.v. infusion of esomeprazole or cimetidine and in addition, the safety assessment of high dose i.v. infusion of esomeprazole will also be an important objective of the study. The study will be performed in approximately 20 centres in China. Each centre is expected to randomise at least 10 patients and the plan is to randomise 200 evaluable patients over a 2-years time period. To reach this number of randomised patients, the number of enrolled patients with upper gastrointestinal bleeding is estimated to be at least 600.

The visit structure of the study is indicated below in Figure 1.

Figure 1 Study flow chart



Visit design

Visit 1 - Enrolment and randomisation phase:

To be enrolled in the study, patients should have an acute upper gastrointestinal bleeding (haematemesis, melaena or haematochezia) or such signs within the last 24 hours, as judged

by the investigator. For the patients to be randomised, a single bleeding source (patients with multiple bleeding ulcers are not to be included in the study) should be endoscopically confirmed to come from either a gastric or duodenal peptic ulcer classified as Forrest Ia, Ib, IIa, or IIb (see Section 4.1). The source of bleeding should be photographed (see Section 6.2.3) and successfully treated by endoscopic treatment (see Section 4.1). The primary endoscopic treatment should be performed **as soon as possible to allow start of i.v. treatment within 24 hours** after first presentation to the hospital. The date and time of first presentation to hospital will be recorded in the electronic Case Report Form (eCRF). If the patient is already hospitalised, i.v. treatment should be started after endoscopic treatment within 24 hours after the first sign or symptom of upper gastrointestinal bleeding.

The following activities and assessments will be done during the enrolment and randomisation phase (Visit 1):

- Admission to hospital
- Signs of bleeding
- Informed consent
- Check inclusion and exclusion criteria
- Allocation of enrolment code (E-code)
- Pregnancy test in female patients with childbearing potential
- Demography
- Electrocardiogram (ECG)
- Vital signs (pulse and blood pressure (BP))
- American Society of Anaesthesiologist's physical status (ASA) class
- Concomitant medication
- Clinical laboratory tests (local lab), see Section 6.4.5
- Endoscopy including Forrest class, treatment and photo documentation
- Serious Adverse Events (SAEs)
- Randomisation

Visit 2 - Administration of Investigational Product phase:

The following assessments will be done **after** randomisation but **before** start of the i.v. treatment:

- Serious Adverse Events (SAEs)
- Medical and surgical history
- History of gastrointestinal disease
- Concomitant medication
- Weight and height (patient should be asked if exact measurement is not feasible)
- Nicotine use
- Physical examination (general appearance, cardiovascular, respiratory, abdomen and neurological system)
- Clinical laboratory tests including *H.pylori* serology (central lab), see Section 6.4.5
- Vital signs (pulse and BP)
- Confirmation of no signs of rebleeding since endoscopy

Eligible and randomised patients will be treated with one of the following two treatment regimens (see Figure 1):

- 80 mg esomeprazole i.v. given as a bolus infusion during 30 min followed by an i.v. continuous infusion of 8 mg per hour during 71.5 hours
- 200 mg cimetidine i.v. given as a bolus infusion during 30 min followed by an i.v. continuous infusion of 60 mg per hour during 71.5 hours

Note: Patients with estimated glomerular filtration rate (eGFR) 30-50 ml/min x 1.73m^2 will be given 200 mg cimetidine i.v. as a bolus infusion during 30 min followed by an i.v. continuous infusion of 30 mg/hour during 71.5 hours.

During the i.v. treatment phase, the patients will be closely monitored with assessments including:

- Vital signs (pulse and BP) (every 8 hour)
- Hb and Hct (local lab) (every 8 hour)
- Creatinine (local lab) (after 24 and 48 hours)

- Adverse events (AEs) (every 24 hours)
- Clinical signs of rebleeding (see Section 6.3.1.1)
- Concomitant medication
- Clinical laboratory tests (central lab) after end of the i.v. treatment, see Section 6.4.5

After completion of the 72 hours i.v. treatment, all patients will receive open label oral treatment with 40 mg esomeprazole once daily for 27 days. The patient could be discharged from hospital when clinical situation permits. Each patient will be informed about signs of rebleeding and will be asked to contact the investigator for an unscheduled visit if there is a suspicion of a rebleeding event.

If the patient reaches the events of significant rebleeding, endoscopic re-treatment and/or surgery due to rebleeding during the i.v treatment phase, study treatment will be stopped and the patient will be treated according to local guidelines. The patient should continue the study and when the clinical situation permits, oral treatment with esomeprazole tablets 40 mg should be initiated and continue to the follow up visit. If i.v. treatment is stopped due to other reason, eg technical failure, double-blind treatment should be re-initiated as soon as the clinical situation permits.

If the patient reaches the events of significant rebleeding, endoscopic re-treatment and/or surgery due to rebleeding during the open label esomeprazole 40 mg q.d. treatment phase, study treatment will be temporarily stopped and the patient will be treated according to local guidelines. The patient should continue the study and when the clinical situation permits oral treatment with esomeprazole tablets 40 mg should be restarted and continue to the follow up visit.

Visit 3 - Follow-up visit:

At the follow-up visit 30(+5) days after start of i.v. treatment, the assessments to be performed include:

- AEs
- Vital signs (pulse and BP)
- Physical examination
- Clinical laboratory tests (central lab), see Section 6.4.5
- Hb and Hct (local lab)
- Concomitant medication

- Discharge from hospital

For all patients with diagnosed gastric ulcers, where an underlying malignancy has not been excluded, or in case *H. pylori* infection has been detected, normal hospital routines should be adhered to after the final visit, as judged by the investigator.

If any transfusion (whole blood, packed red cells, plasma or platelets) or surgery has been done during the course of the study, the appropriate sections in the eCRF should be completed.

Unscheduled visits

An unscheduled visit should be performed in the event of a rebleeding event or patient discontinuation of the study or Investigational Product (IP). The following assessments will be performed during the unscheduled visit as applicable:

- Admission to hospital
- AEs
- Clinical signs of rebleeding
- Endoscopy including Forrest class, treatment and photo documentation
- Vital signs (pulse and BP)
- Physical examination
- Concomitant medication
- Discharge from hospital
- Hb and Hct (local lab)
- Clinical laboratory tests (central lab), see Section 6.4.5

If any blood transfusion or surgery has been done during the course of the study, the appropriate sections in the eCRF should be completed.

Table 1 Study Plan

Visit No.	1	2	3
Visit description	Enrolment and randomisation phase	Administration of IP phase	Follow-up visit
Visit window	0-24 h after admission	0-72 h after start of i.v. treatment & 27 days oral treatment	Day 30 (+5) after start of i.v. treatment
Informed consent	X		
Inclusion / exclusion criteria	X		
Allocation of E-code	X		
Demography	X		
ASA class	X		
Vital signs (pulse, BP)	X	X[1]	X
Endoscopy, Forrest class and photo	X[2]		
Endoscopic treatment	X		
Hb and Hct (local lab)	X	X[3]	X
APTT, PTC and platelets (local lab)	X		
Creatinine (local lab)	X	X[4]	
Pregnancy test	X[5]		
ECG	X		
Concomitant medication	X	X	X
Randomisation	X[6]		
AE recording	X[7]	X[8]	X
H. Pylori serology		X[9]	
Medical / surgical history		X	
Physical examination		X	X
Weight / height		X	
Any signs of rebleeding		X[10]	
Distribution of IP		X[11]	
Laboratory assessment (central lab)		X[12]	X

1. Vital signs will be closely monitored every 8 hours during i.v. treatment phase.
2. Photo document should aim to visualise signs of ongoing or previous bleeding of peptic ulcer. (see Section 6.2.3)

3. Hb and Hct will be tested in local lab every 8 hours during i.v. treatment phase.
4. Creatinine will be tested after 24 and 48 hours during i.v. treatment phase.
5. Pregnancy test applicable for women of child-bearing potential.
6. After the endoscopy.
7. From obtained informed consent until first administration of IP, only SAEs will be collected.
8. From first administration of IP, AEs should be collected every 24 hours during i.v. treatment phase.
9. To be done before start of i.v.treatment.
10. The investigator must verify that there are no signs of rebleeding at the time when the i.v. treatment starts. (see Section 6.3.1.1)
11. After completion of the 72 hour i.v.treatment, all patients will receive open label oral treatment with 40 mg esomeprazole once daily for 27 days.
12. To be done before and after i.v.treatment.

3.2 Rationale for study design, doses and control groups

The study will be conducted in patients with bleeding from a gastric or a duodenal ulcer and in whom there is a high risk of a clinically significant rebleeding (as indicated by endoscopic signs Forrest Ia-IIb) after the initial bleeding has been successfully treated endoscopically. Such a relapse of bleeding may be life threatening, requiring additional diagnostic and therapeutic interventions and result in prolonged hospital stay. Due to lack of feasibility in China to, within a reasonable time frame, successfully conduct a statistically sized efficacy study with sufficient number of events to allow formal statistical efficacy analysis in the target population, this study will primarily be descriptive. However, the sample size is based on Chinese regulations to collect safety data from 100 pairs in a randomised fashion.

The rate of clinically significant rebleeding during the first 72 hours after initial successful endoscopic haemostatic therapy is the primary efficacy variable, which could be regarded as representing also an important safety consideration for patients. The rationale for primarily assessing rebleeding rate at 72 hours rather than at 7 days, as recommended by an International Consensus Conference (Laine et al 2010) for methodology in studies in nonvariceal upper gastrointestinal bleeding, is to be consistent with the global PUB study in which high dose i.v. esomeprazole was used. In addition, the outcome during 72 hours will more closely reflect the effect of the i.v. treatment. However, the rate of rebleeding during the first 7 and 30 days, respectively, is also included as secondary variables. This is done in order to determine if there is a prolonged beneficial effect of i.v. esomeprazole also during the first days after the end of the 72 hours infusion period, and if the effect of initial i.v. esomeprazole can be maintained also during a longer observation period while all patients participating in the study are receiving oral esomeprazole 40 mg daily. Additional outcome variables measure the extent of other interventions ie, rate of endoscopic re-treatment, surgery and blood transfusions, all of which may be related to rebleeding.

The rationale for using high dose i.v. esomeprazole is based on *in vitro* studies as well as clinical studies. In vitro studies indicated that the blood coagulation system is highly sensitive to the lowering of pH. Clotting time was prolonged and platelet disaggregation was increased at lower pH (Green et al 1978, Patchett et al 1989), and it has therefore been suggested that an early and pronounced reduction of intragastric acidity would reduce the frequency of rebleeding from peptic ulcers (Lau et al 2000). The global placebo controlled PUB study has confirmed that pronounced reduction of intragastric acidity achieved by high dose esomeprazole i.v. regimen resulted in reduced frequency of rebleeding from peptic ulcers as compared to placebo (Sung et al 2009).

An initial i.v. bolus dose of 80 mg esomeprazole will be given in order to reduce acidity in the stomach as rapidly as possible, thereby favouring haemostasis. In dose-finding experiments in a Western population of healthy patients (AZ study D9615C00015) a bolus dose of 80 mg was shown to be superior to a dose of 40 mg, whereas a dose of 120 mg was not more effective than 80 mg. The same study also showed that an infusion rate of 8 mg/hour was significantly more effective in reducing intragastric pH than 4 mg/hour. In a PK/PD study with i.v. esomeprazole in Chinese healthy patients (AZ study D9615L00007) the average PD effect

was similar between 40 mg and 80 mg bolus dose, respectively, and between the infusion rate of 4 mg/hour and 8mg/hour, respectively. The Chinese PK/PD study population consisted of 10% poor metabolizers and 55% heterozygous extensive metabolizers, which might have reduced the differentiation between the lower and higher dosing regimens. The chosen infusion rate (8 mg/hour) in this study is expected to maintain highly effective acid inhibition throughout the infusion period regardless of CYP2C19 genotype and has not raised any safety concern when used in the global PUB study. Doses higher than 8 mg/h are not considered, due to limited clinical safety documentation for such doses.

Intravenous treatment will be given for 72 hours (3 days). This duration of treatment is sufficiently long to cover the period in which most rebleedings occur and has also demonstrated clinical efficacy in the global PUB study. An extension of the i.v. treatment duration above 3 days would prolong the hospitalisation, with little further expected gain in reduction of rebleeding (Lau et al 2000). The aim of the oral treatment with esomeprazole 40 mg q.d. for an additional 27 days in both treatment arms is to maintain a reduced acidity in the stomach, thereby optimising haemostasis and ulcer healing and minimizing the risk of further ulcer development. Esomeprazole 40 mg q.d. is chosen, as it is the highest oral dose approved, and to ensure ulcer healing after a bleeding episode this dose is considered clinically well justified.

High dose esomeprazole i.v. regimen is the only treatment with regulatory approval for prevention of rebleeding of PUB after endoscopic treatment, however, not approved in China. In this situation another placebo-controlled PUB study would be inappropriate from an ethical perspective and thus an active control pharmaceutical treatment reducing gastric acid secretion is limited to the use of H2RA and PPI products. Cimetidine bolus injection of 200 mg during 0.5 hour followed by continuous i.v. infusion of cimetidine 60 mg/hour for additional 71.5 hours was chosen as active control in this study. The rationale for choosing Cimetidine i.v. is that this drug is approved for treatment of peptic ulcer bleed in China (however, not specifically for prevention of rebleeding after endoscopic treatment) and i.v. doses up to a total of 2g per 24 hours and infusion rate up to 75mg/hour is compatible with the label for cimetidine in China. Similar i.v. dosing regimen (300 mg bolus and 50 mg/hour) as used in this study has been shown to provide profound acid suppression during short time use (mean percentage of time with pH >4 of 82% day 1 and of 72% day 2) in critically ill patients (Somberg et al 2008) and is considered safe by Food and Drug Admmission (FDA) and therefore approved in US for stress ulcer prophylaxis indication. Using cimetidine i.v. bolus and continuous infusion will facilitate keeping the treatments blinded and simplify the conduct of the study. The need for using a drug with insufficient documentation of efficacy as active control will cause uncertainty in the assessment of the efficacy of high dose esomeprazole i.v. regimen in a setting with small sample size. However, the study will provide valuable data on the safety and tolerability of this treatment in a Chinese PUB patient population.

4. PATIENT SELECTION CRITERIA

Investigator(s) should keep a record, the patient screening log, of patients who entered pre-study screening and record enrolled as well as not enrolled patients' information including reasons for not being enrolled.

Each randomised patient should meet all of the inclusion criteria and none of the exclusion criteria for this study. Under no circumstances can there be exceptions to this rule.

4.1 Inclusion criteria

For inclusion in the study patients should fulfil the following criteria:

1. Provision of informed consent prior to any study specific procedures.

2. Female or male aged ⩾18 years and ⩽70 years.

3. Acute upper gastrointestinal bleeding (haematemesis, melaena or haematochezia) or such signs within the last 24 hours as judged by the investigator.

4. One endoscopically confirmed bleeding gastric or duodenal peptic ulcer, at least 5 mm in diameter, classified as Forrest Ia, Ib, IIa, or IIb. Photo documentation of the source of bleeding should be provided (detail in section 6.2.3).

   Forrest classification of PUB (Forrest et al 1974):
   Ia = arterial bleeding
   Ib = oozing bleeding
   IIa = non-bleeding visible vessel
   IIb = adherent clot

   In case of Forrest IIb (adherent clot), efforts should be made to remove the clot. If the clot cannot be removed, the patient should be included as Forrest IIb.

5. Successful haemostasis (which is considered to have been established if bleeding has stopped and, if applicable, formerly bleeding vessels are flattened or cavitated) achieved by endoscopic treatment and confirmed by site staff with:

   – Injection therapy (epinephrine, dilution 1:10000)

and/or one of the following:

   – Coagulation with heater probe

   – Electrocautery

   – Haemoclips

4.2 Exclusion criteria

Patients should not enter the study if any of the following exclusion criteria are fulfilled:

1. Malignancy or other advanced disease with a life expectancy of < 6 months as judged by the investigator.

2. The ASA classification (Appendix F) of physical status ⩾ 4 as judged by the investigator.

3. Severe hepatic disease defined as Child-Pugh B or C (Appendix D).

4. Severe renal disease, defined as eGFR of less than 30 ml/min x 1.73m^2 using the simplified Modification of Diet in Renal Disease (MDRD) formula:

$$\begin{aligned}\text{eGFR [mL/min/1.73m}^2\text{]} = 186.3 &\times (\text{serum creatinine [mg/dL]})^{-1.154} \\ &\times (\text{age [years]})^{-0.203} \\ &\times (0.742, \text{if female}) \\ &\times (1.210, \text{if African American})\end{aligned}$$

5. Major cardiovascular event at enrolment or within 3 months prior to enrolment such as stroke, myocardial infarction, or hospitalisation for treatment of unstable angina pectoris as judged by the investigator.

6. Haemorrhagic disorder, platelets <100x10^9/L, INR>1.5, APTT>1.5x upper limit of normal (ULN), or treatment with low-molecular weight heparin.

7. Endoscopic suspicion of gastric malignancy or juxta pyloric stenosis as judged by the investigator.

8. Sign of multiple bleeding peptic ulcers or concomitant other gastrointestinal bleeding from esophageal varices, reflux esophagitis, gastritis, Mallory Weiss rifts, ulcus simplex, Dieulafoy's lesion, colon, small bowel, or ulcer distal to the stoma in Billroth-resected patients.

9. Need for treatment during the first 7 days of the study with NSAIDs, Cyclooxygenase-2 (COX-2) inhibitors, acetyl salicylic acid (ASA) (including low dose) or clopidogrel.

10. Known or suspected hypersensitivity to any component of any PPI (esomeprazole, omeprazole, lansoprazole, rabeprazole, dexlansoprazole or pantoprazole) or to Cimetidine.

11. Planned treatment with: warfarin (including other vitamin K antagonists), cisapride, phenytoin, atazanavir, nelfinavir, digoxin, methotrexate, clopidogrel, tacrolimus, teophyllin, lidocaine, nifedepine.

12. Chemotherapy or radiation therapies within 2 weeks prior to randomisation or planned during the course of the study.

13. Pregnancy, planned pregnancy or lactation. Women of childbearing potential must use reliable and medically accepted methods of birth control, as judged by the investigator.

14. Known or suspected alcohol, drug or medication abuse.

15. Any condition associated with poor compliance as judged by the investigator.

16. Participation in any study involving administration of an IP or device within the preceding 30 days prior to enrolment.

17. Involvement in the planning and conduct of the study (applies to both AstraZeneca staff and staff at the investigational site).

18. Previous enrolment in the present study.

Procedures for withdrawal of incorrectly enrolled patients see Section 5.3

5. STUDY CONDUCT

5.1 Restrictions during the study

5.1.1 Restrictions concerning endoscopy

The following restrictions will be applied for patients participating in the study:

- Endoscopic treatment with modalities not mentioned in Section 4.1, inclusion criteria No. 5, eg, argon plasma coagulation, injection of water, thrombin, fibrin glue or sclerosing agents (lipidocanol, ethanol), is not allowed.

- "Second look" endoscopy without clinical signs of rebleeding as defined in Section 6.3.1.1 is not allowed to avoid misclassification of non-significant rebleeding.

5.1.2 Restrictions concerning *H.pylori* treatment

Treatment of *H. pylori* infection is not allowed during the study. In case *H. pylori* infection has been detected, normal hospital routines should be adhered to, after the final visit, as judged by the investigator.

5.1.3 Restrictions regarding concomitant medications

For more details, see Section 5.6

5.2 Patient enrolment, randomisation and initiation of investigational product

It is each Principal Investigator´s (PI) responsibility to:

1. Obtain signed informed consent from the potential patient before any study specific procedures are performed.

2. Assign potential patient a unique E-code.

3. Determine patient eligibility. See Sections 4.1 and 4.2

4. Allocate a unique randomisation code to an eligible patient.

5. Inform unblinded nurse of unique randomisation code to prepare infusion bag and ensure first administration of blinded IP occurs within the time frame. See Section 5.5

6. Inform the unblinded nurse about any patient with eGFR 30- 50 ml/min x 1.73m^2 in need of dose reduction of cimetidine during the continuous infusion phase.

7. Ensure the compliance of IP administration.

5.2.1 Procedures for randomisation

A patient who signs the Informed Consent Form (ICF) will be allocated with an E-code by Interactive Voice Response System (IVRS)/Interactive Web Response System (IWRS). The patient should receive the lowest E-code available at the centre. Patient eligibility will be established before treatment randomisation. Re-screening is not allowed in the study.

A patient who fulfil all inclusion criteria and meet none of the exclusion criteria will be allocated a randomisation code accordingly by IVRS/IWRS to one of the treatment arms in an equal proportion within each site.

Randomisation code will be assigned strictly sequentially as the patients become eligible for randomisation. If a patient has been withdrawn from participation in the study, he/she cannot re-enter into the study. If a patient withdraws from participation in the study, then his/her enrolment/randomisation code cannot be reused.

5.3 Procedures for handling patients incorrectly enrolled, randomised or administered investigational product

Patients who fail to meet the inclusion/exclusion criteria should not, under any circumstances, be enrolled or randomised to receive IP. There can be no exceptions to this rule.

Where patients that do not meet the selection criteria are enrolled in error or incorrectly started on treatment, or where patients subsequently fail to meet the study criteria post initiation, the investigator should inform the AstraZeneca study physician or delegate immediately.

Patients who are incorrectly enrolled but are not yet randomised or initiated on treatment should be withdrawn from the study. In the event that a patient has been randomised and administration of study medication has started in error despite best efforts to ensure that the inclusion and exclusion criteria were adhered to by the investigator, with respect to continuing administration of study medication, medical judgment should apply on a case-by-case basis.

The likely benefits and risks to the patient should be assessed and a discussion should occur between the study physician and the investigator regarding whether to continue or discontinue the patient from treatment.

In cases where it could not be excluded that exposure to IP might compromise individual safety of the specific patient, the administration of IP must be stopped. Otherwise, the patient may continue on study treatment. In situations where an agreement cannot be reached, the patient should have the IP stopped. If decided to stop the intake of IP, the procedures described in Section 5.8.1 must be followed.

The AstraZeneca physician is to ensure all such contacts are appropriately documented.

5.4 Blinding and procedures for unblinding the study

5.4.1 Methods for ensuring blinding

The Sponsor, Investigators, study staff participating in patient care or clinical evaluations, and patients will be blinded to IP assignment.

The treatment allocation will be kept strictly within ublinded nurses to safeguard the integrity of the blinding of Investigators and patients, and hence to minimize any possible bias in data handling.

5.4.1.1 Unblinded nurse and unblinded monitor

The approach of using an unblinded nurse at hospital is a way to ensure blinding throughout the study. The unblinded nurse will be responsible for preparing the blinded IP. The open labelled esomeprazole powder and cimetidine solution for the double blinded infusion treatment phase will be packed in separated boxes. Only the unblinded nurse can open the boxes. The open labelled esomeprazole powder and cimetidine solution will be properly prepared by the unblinded nurse and put into a blinded labelled infusion bag before use by the blinded nurse, according to the separate instructions. The unblinded nurse must not participate in the care of patients. In addition to the blinded monitor, AstraZeneca will assign an unblinded monitor (see Section 9.3) to confirm drug accountability. The unblinded monitor must not be involved in other parts of the study conduct.

5.4.1.2 The site patient randomisation list / code envelope

The site patient randomisation list is a document with a set of the randomisation codes which are pre-allocated to the hospital.

The individual code envelope will indicate the treatment arm for each randomised patient.

The site patient randomisation list / the individual code envelope will be provided to the unblinded nurse only for the preparation of the blinded labelled infusion bag. The unblinded monitor will access the site patient randomisation list / the individual code envelope during the site drug accountability monitoring activities. The information in the site patient randomisation list / the individual code envelope must be kept strictly from other personnel involved in the conduct of the study, and at a secure location until the end of study.

5.4.2 Methods for unblinding the study

The eligible patient will be randomised with a unique individual randomisation code. The individual randomisation code must not be broken by the investigator(s) or study staff except in medical emergencies when the appropriate management of the patient requires knowledge of the treatment randomisation. If any blinded information is broken, the date, the time and the reason must be documented / recorded via IVRS/IWRS and in any associated AE report. The investigator is responsible for ensuring this documentation is maintained and reports the action to AstraZeneca, without revealing the treatment given to the patient and the blinded AstraZeneca staff.

AstraZeneca retains the right to break the randomisation code for SAEs that are unexpected and are suspected to be causally related to an IP and that potentially require expedited reporting to regulatory authorities.

Randomisation codes will not be broken for the planned analyses of data until all decisions on the evaluability of the data from each individual patient have been made and documented.

Except for safety reasons, patients, investigators, all blinded site staff and blinded monitors will have no access to the individual treatment allocation until after the finalization of the Clinical Study Report (CSR).

5.5 Treatments

5.5.1 Identity of investigational product(s)

The IPs to be used in the study are described in Table 2. Each vial of esomeprazole and each ampoule of cimetidine will be labelled and packed into labelled boxes. Commercial available Esomeprazole tablets will be used and labelled with study specific labels.

Table 2 Investigational Product

Product Name	Dosage form and strength	Manufacturer
Esomeprazole (Nexium®)	Powder for solution for infusion, 40 mg (as esomeprazole sodium 42.5 mg)	AstraZeneca
Cimetidine (Tagamet®)	Solution for infusion, 200mg	
Esomeprazole (Nexium®)	Tablet, 40 mg (as esomeprazole magnesium trihydrate 22.3 mg)	AstraZeneca

5.5.2 Doses and treatment regimens

For eligible patients randomisation followed by i.v. treatment with IP, either esomeprazole or cimetidine should start as soon as possible after the initial primary haemostasis. Start of i.v. treatment must occur within 24 hours after first presentation to the hospital. If the patient is already hospitalised, i.v. treatment should be started within 24 hours after first sign or symptom of upper gastrointestinal bleeding. The 72 hours randomised i.v treatment is followed by a 27 days oral treatment with esomeprazole tablets 40 mg.

If the patient reaches the events of significant rebleeding, endoscopic re-treatment and/or surgery due to rebleeding during the i.v treatment phase, study treatment will be stopped and the patient will be treated according to local guidelines. The patient should continue the study and when the clinical situation permits oral treatment with esomeprazole tablets 40 mg should be initiated and continue to the follow up visit. If i.v. treatment is stopped due to other reason, eg technical failure, double-blind treatment should be re-initiated as soon as the clinical situation permits.

If the patient reaches the events of significant rebleeding, endoscopic re-treatment and/or surgery due to rebleeding during the open label esomeprazole 40 mg q.d. treatment phase, study treatment will be temporarily stopped and the patient will be treated according to local guidelines. The patient should continue the study and when the clinical situation permits oral treatment with esomeprazole tablets 40 mg should be restarted and continue to the follow up visit.

5.5.2.1 Randomised i.v. treatment

During the 72 hours i.v. treatment each randomised patient will receive one of the following treatment regimens:

Esomeprazole treatment:

Esomeprazole i.v.	Given as 80 mg bolus infusion during 30 min
Esomeprazole i.v.	8 mg/h constant infusion during 71.5 hours

Cimetidine treatment:

Cimetidine i.v.	Given as 200 mg bolus infusion during 30 min
Cimetidine i.v.	60 mg/h constant infusion during 71.5 hours

Both the esomeprazole powder for solution for infusion and cimetidine solution for infusion will be reconstituted with 0.9% sodium chloride solution for infusion (supplied by clinical sites) and put into 100 ml infusion bag before use, to ensure a final volume of 100 ml. Detailed handling instructions regarding preparation of infusion solution will be provided by AstraZeneca.

For the 30 minutes i.v. treatment, the entire volume of one bag (corresponding to 80 mg esomeprazole or 200 mg cimetidine) will be administered i.v. at a rate of 200 ml/h. The constant rate infusion will be administered i.v. at a rate of 10 ml/h over 71.5 hours. During the constant rate infusion, the infusion bag (corresponding to 80 mg esomeprazole or 600 mg cimetidine) should be changed every 9 (± 1) hours. The prepared solution can be kept at below 30 degrees in normal in-door light up to 12 hours. In order to ensure blinding, the prepared solution not used within 12 hours from preparation must be returned to the unblinded nurse.

5.5.2.2 Oral treatment with esomeprazole 40 mg

After the i.v. treatment, all patients will be treated orally with esomeprazole 40 mg tablet once daily for 27 days.

If the infusion is terminated before 8.00 a.m. the first oral dose is given the same day. If the infusion is terminated after 8.00 a.m. the first oral dose is given the next day in the morning.

The esomeprazole tablets should be taken before breakfast with a glass of water. The tablets must not be chewed, crushed or divided, but should be swallowed whole.

5.5.3 Dose Adjustment

In the patients with eGFR 30-50 ml/min x 1.73m^2, the cimetidine constant infusion dose should be reduced to 30 mg/h, which means only half the amount of cimetidine (300 mg) should be added to the infusion bag in order to keep the infusion rate the same (10 ml/ h). The i.v. bolus dose of cimetidine (200 mg) should not be changed. It is the investigator´s responsibility to make sure that the unblinded nurse receives the information about the need for dose adjustment of cimetidine before the IP preparation.

5.5.4 Labelling

Labels will be prepared in accordance with Good Manufacturing Practice (GMP) and local regulatory guidelines. The labels will fulfil GMP Annex 13 requirements for labelling. Label text will be translated into local language.

Packing and labelling will be carried out at

Each vial and ampoule will be labelled with an unblinded tear-off label. The tear-off part is to be inserted into the source data documentation, which is only accessable for the unblinded nurse and unblinded monitor. The IP boxes with esomeprazole vials and cimetidine ampoules and the commercial boxes with esomeprazole tablets will be labelled with an unblinded single panel label. For the infusion bags, blinded tear-off labels will be provided together with the IP boxes of esomeprazole vials and cimetidine ampoules. The infusion bag will be supplied by the clinical sites and the unblinded nurse will put the blinded tear-off label on the infusion bag after the preparation.

5.5.5 Storage

All IPs should be kept in a secure place under appropriate storage conditions. A description of the appropriate storage and shipment conditions are specified on the IP label and in the IB.

5.6 Concomitant and post-study treatment(s)

The following concomitant medications and treatments are not allowed **prior** to enrolment:

- Chemotherapy or radiation therapies within 2 weeks prior to enrolment.

The following concomitant medications and treatments are not allowed **after enrolment** and **during** the study:

- As they interfere with the disease under study:
  - PPIs or H2RAs (other than IP), sucralfate, and prostaglandins
  - Somatostatin and tranexamic acid or drugs with similar effect
  - Heparin
  - NSAIDs, COX- 2 inhibitors and ASA (including low dose) during the first 7 days of the study
  - Treatment of *H. pylori* infection. In case *H. pylori* infection has been detected, normal hospital routines should be adhered to, after the final visit, as judged by the investigator
- As there is a potential risk for drug-drug interactions with esomeprazole or cimetidine:
  - Warfarin (including other vitamin K antagonists), cisapride, phenytoin, atazanavir, nelfinavir, digoxin, methotrexate, clopidogrel, tacrolimus, teophyllin, lidocaine, nifedepine
- Due to patient vulnerability:

  - Chemotherapy or radiation therapy

- To avoid non-significant bleeding being classified as rebleeding:
  - "Second look" endoscopy without clinical signs of rebleeding as defined in Section 6.3.1.1

Other medication, which is considered necessary for the patient's safety and well-being, may be given at the discretion of the investigator(s). The administration of all medication (including IPs) must be recorded in the appropriate sections of the eCRF. Endoscopy-related anaesthetic and sedative medication given according to normal routines should not be recorded in the eCRF.

If the patient reaches the events significant rebleeding, endoscopic re-treatment and/or surgery due to rebleeding, treatment will be stopped and the patient will be treated according to local guidelines. Restrictions for concomitant medications and treatments are not applicable in such cases. When the clinical situation permits， oral treatment with esomeprazole 40 mg tablets should be initiated/re-started.

5.7 Treatment compliance

The administration of all IPs should be recorded in the appropriate sections of the eCRF.

The i.v. treatment will be administered under the supervision of the study site personnel. The actual times of start and stop (and, if applicable, any stop and restart in between) as well as the infused volume and the infusion rate of the i.v. infusion, will be recorded in the eCRF.

During the open label oral treatment with esomeprazole 40 mg tablets, the patients will record intake of IP in the patient diary on a daily basis, and the investigator or delegate will check adherence to prescribed treatment at study visits.

Each patient is required to comply with the prescribed treatment regimen throughout the study and should be counselled on the importance of taking their IP as prescribed. The patients will be instructed to return all unused tablets at the follow-up visit/final visit. The tablet counts will be recorded in the eCRF.

5.7.1 Accountability

The IPs provided for this study will be used only as directed in the protocol.

It is the PI's responsibility to ensure that a procedure is established and maintained for the operation of the blinded and the unblinded IPs. This includes but is not limited to:

- The IPs are administrated only by the site staff named in the delegation of responsibility log.

- The unblinded nurse will account for the IP accountability including the IP acknowledge receipt at the site, the infusion bag preparation, the i.v. IP reconciliation and the drug destruction. Any discrepancies should be documented, investigated, and appropriately resolved
- The blinded nurse/site staff will be responsible for oral IP reconciliation.
- The blinded nurse will account for all IPs dispensed to and returned from the patient. The unused oral IP will be returned back to unblinded nurse after the reconciliation by blinded monitor.
- After i.v. administration, the used infusion bags will be returned back to the unblinded nurse and discarded according to hospital routines as soon as possible or at latest at the end of the day.

All used and un-used IPs will be sent back to local vendor for destruction according to local procedure. Destruction must not take place unless the responsible person at AstraZeneca has approved it.

The unblinded monitors will ensure the drug accountability record at clinical sites is maintained accurately.

5.8 Discontinuation of investigational product

Patients may be discontinued from study treatment at any time. Reasons for discontinuing a patient from IP may be:

- Patient decision. The patient is at any time free to discontinue treatment, without prejudice to further treatment
- Safety reasons as judged by the investigator and/or AstraZeneca (eg, histologically confirmed malignancy if routine biopsies were taken at visit 1)
- Adverse event, including event of rebleeding
- Eligibility criteria not fulfilled (see Section 5.3)
- Severe non-compliance to protocol as judged by the investigator and/or AstraZeneca
- Other reason specified by the investigator or AstraZeneca

If the patient is discontinued from IP, the scheduled study visits, data collection and procedures should continue according to the CSP until the follow-up visit. Alternatively, if the patient does not agree to this option, a modified follow up through e.g. telephone contact at the time-point of the follow-up visit should be arranged, if agreed to by the patient and in compliance with local data privacy laws/practices.

5.8.1 Procedures for discontinuation of a patient from investigational product Discontinuation of treatment

If the study treatment is stopped, an unscheduled visit in the eCRF should be completed. After this visit, the patient should come for the follow-up visit on day 30(+5) and the assessments specified for the follow-up visit (Visit 3) should be completed and recorded in the eCRF. In addition to this, information regarding the event rebleeding, surgery and blood transfusion must be entered in the eCRF.

5.9 Withdrawal from study

Patients are at any time free to withdraw from study (IP and assessments), without prejudice to further treatment (withdrawal of consent). Such patients will always be asked about the reason(s) and the presence of any AE. If possible, they will be seen and assessed by an investigator and the assessments specified for the final visit should be completed and recorded in the eCRF. Patient diary and all IPs should be returned by the patient. AEs will be followed up by the investigator for as long as medically indicated, but without further recording in the eCRF (see Sections 6.4.3 and 6.4.4).

Reasons for withdrawal from the study may include, but are not limited to

- Patient decision. The patient is at any time free to discontinue their participation in the study, without prejudice to further treatment.
- Eligibility criteria not fulfilled
- Death
- AE
- Severe non-compliance with protocol, defined as refusal or inability to adhere to the CSP requirement
- Patient lost to follow-up
- Other, with specification given.

Withdrawn patients will not be replaced. For all patients who have received IP but have discontinued from the study, the investigator should make every possible effort to check that the patient is not reported dead within 30 days after randomisation.

6. COLLECTION OF STUDY VARIABLES

6.1 Recording of data

The system will be used for data collection and query handling. The investigator will ensure that data are recorded on the eCRF as specified in the CSP and in accordance with the instructions provided.

The investigator ensures the accuracy, completeness, and timeliness of the data recorded and of the provision of answers to data queries according to the Clinical Study Agreement (CSA). The investigator will sign the completed eCRFs. A copy of the completed eCRFs will be archived at the study site.

6.2 Data collection at enrolment and follow-up

Refer to Section 3.1

6.2.1 Enrolment procedures

Refer to Section 3.1

6.2.2 Follow-up procedures

Refer to Section 3.1

6.2.3 Photo documentation

Photo documentation, according to normal hospital routines, is required as source documentation and must be available in duplicate (as colour printouts, or images/video clips in electronic format on videotape, CD, DVD). All possible efforts should be made to document the peptic ulcer on the photos, and the investigator should aim to visualise signs of ongoing or previous bleeding during enrolment and in case of rebleeding. Lack of photo documentation can only be accepted during night time endoscopies, performed with emergency endoscopes without photo equipment. A label supplied by AstraZeneca should be attached to the back of the printouts (other forms of photo documentation are labelled correspondingly). The label will contain E-code and the date of endoscopy.

One copy of the photo documentation will be stored in the investigators study file and the other will be sent to AstraZeneca R&D, Mölndal. Explorative analyses of random samples of photos will be done during the study, in order to ensure photo quality and consistency in applying the Forrest classification between the various study centres.

6.3 Efficacy

6.3.1 Clinically significant rebleeding within 72 hours, 7 and 30 days

6.3.1.1 Methods of assessment

The diagnosis of a rebleeding could be based on either A, B or C (Table 3).

The recommendation is to always confirm the diagnosis of rebleeding by endoscopy. However, if no bleeding can be detected at re-endoscopy the patient will be defined as a rebleeding if he/she fulfils C (vomiting >200 ml of fresh blood) and/or B.

Table 3 Diagnostic criteria for clinically significant rebleeding

	Rebleeding diagnosed by:	Criteria for diagnosis
A	**Endoscopy** – initiated by clinical signs of bleeding defined as: one of B1 or B2 or B3 and endoscopic verification, ie one of A1 or A2 It is the result of the endoscopy that defines if there is a rebleeding or not	**A1** Blood in stomach (this criteria cannot be used during the first 6 hours after primary endoscopic haemostasis). **A2** A verified active bleeding from a peptic ulcer (Forrest Ia, Ib).
B	A true **clinically** based definition, at least two of B1 and/or B2 and/or B3	**B1** Vomiting of fresh blood or fresh blood in a gastric tube or haematochezia or melaena after a normal stool. **B2** Decrease in Hb >20g/L (or Hct >6%) during 24 hours or an increase in Hb <10g/L (or Hct <3%) despite ≥2 units of blood has been transfused during 24hours. **B3** Unstable circulation systolic blood pressure ≤ 90 mmHg or pulse ≥110/min (after have had a stable circulation).
C	**Haematemesis**	**C** Vomiting significant amounts (>200 ml) of fresh blood as estimated by the investigator.

If rebleeding is suspected, an endoscopy is recommended. At the endoscopy, the rebleeding should be photo documented and classified. The Forrest class of the ulcer will be recorded in the eCRF together with date and time for the rebleeding. The time of a clinically significant rebleeding is defined as the time of demonstrating the first clinical sign of a rebleeding (B1, B2 or B3) which is subsequently confirmed by endoscopy (A) or an additional clinical sign (B). In case of an active bleeding endoscopic re-treatment is recommended. Photo documentation of the rebleeding should be sent to AstraZeneca R&D Mölndal, Sweden.

When the patient is discharged from hospital, he/she will receive an information card, detailing which signs and symptoms that might be associated with rebleeding. If the patient experiences any such sign or symptom, he/she should immediately contact the investigator or the hospital, and should be evaluated without delay for the possibility of a rebleeding.

6.3.2 Endoscopic re-treatment within 72 hours and 30 days

6.3.2.1 Methods of assessment

Any endoscopic re-treatment initiated within 72 hours or 30 days that is caused by rebleeding will be recorded in the eCRF.

If rebleeding is suspected (see Section 6.3.1.1), endoscopy is recommended. In case of rebleeding, endoscopic re-treatment is recommended in case the bleeding ulcer is classified as Forrest Ia, Ib, IIa or IIb.

6.3.3 Surgery within 72 hours and 30 days

6.3.3.1 Methods of assessment

Any surgery (except endoscopic treatment) initiated within 72 hours or 30 days that is caused by rebleeding will be recorded in the eCRF.

The decision to perform surgery is based on several factors, such as the patient's age, co-morbidities, primary endoscopic findings, the patient's actual status and the progress of the actual bleeding. In order to get a more uniform base for the decision recommendations on when to perform surgery have been designed. However, it is always the responsible investigator who decides if and when surgery should be performed.

Recommendations for surgery:

- Extensive continuous bleeding as judged by massive haematemesis and /or haematemesis with shock (shock defined as a systolic BP <80 mmHg or decrease >30 mmHg than baseline normal BP, a peripheral pulse >120 beats/min) and when endoscopy treatment is not judged to be an alternative.
- Clinical signs of significant continuous bleeding after 4 units of blood (1 unit whole blood= 200 ml; 1 unit packed red cells= 120 ml) has been given over a period of 24 hours.
- Clinical signs of significant continuous bleeding after in total 8 units of blood (1 unit whole blood= 200 ml; 1 unit packed red cells= 120 ml) has been given.

6.3.4 Number of blood units transfused within 72 hours and 30 days

6.3.4.1 Methods of assessment

The amount of blood components (whole blood, plasma, packed red cells and platelets) transfused to the patient during the study will be recorded in the eCRF.

Recommendations on when to perform blood transfusions have been designed. However, it is always the responsible investigator who decides if and when blood transfusions should be performed.

Recommendations on when to give blood transfusions (whole blood, packed red cells):

Extensive continuous bleeding (as judged by massive haematemesis and/or haematemesis with shock).

- Systolic BP < 90 mmHg or decrease > 30 mmHg than baseline normal BP
- Hb < 70g/L, Hct <25%
- A peripheral pulse >120 beats/min

6.4 Safety

The PI is responsible for ensuring that all staff involved in the study is familiar with the content of this section.

6.4.1 Definition of adverse events

An AE is the development of an undesirable medical condition or the deterioration of a pre-existing medical condition following or during exposure to a pharmaceutical product, whether or not considered causally related to the product. An undesirable medical condition can be symptoms (eg, nausea, chest pain), signs (eg, tachycardia, enlarged liver) or the abnormal results of an investigation (eg, laboratory findings, electrocardiogram). In clinical studies, an AE can include an undesirable medical condition occurring at any time, including run-in or washout periods, even if no study treatment has been administered.

The term AE is used to include both serious and non-serious AEs.

6.4.2 Definitions of serious adverse event

A SAE is an AE occurring during any study phase (ie, run-in, treatment, washout, follow-up), that fulfils one or more of the following criteria:

- Results in death
- Is immediately life-threatening
- Requires in-patient hospitalisation or prolongation of existing hospitalisation
- Results in persistent or significant disability/incapacity or substantial disruption of the ability to conduct normal life functions
- Is a congenital abnormality or birth defect

- Is an important medical event that may jeopardise the patient or may require medical intervention to prevent one of the outcomes listed above

For further guidance on the definition of a SAE, see Appendix B to the CSP.

6.4.3 Recording of adverse events

Time period for collection of adverse events

AEs will be collected from the time of the first administration of IP until the end of study. SAEs will be collected from signed inform consent until the end of the study.

Follow-up of unresolved adverse events

Any AEs that are unresolved at the patient's last visit are to be followed up by the investigator for as long as medically indicated, but without further recording in the eCRF. AstraZeneca retains the right to request additional information for any patient with ongoing AEs/SAEs at the end of study, if judged necessary.

Variables

The following variables will be collected for each AE:

- AE (verbatim)
- The date and time when the AE started and stopped
- Maximum intensity
- Whether the AE is serious or not
- Investigator causality rating against the IP (yes or no)
- Action taken with regard to IP
- AE caused patient's withdrawal from study *(*yes or no*)*
- Outcome

In addition, the following variables will be collected for SAEs:

- Date AE met criteria for SAE
- Date Investigator became aware of SAE
- AE is serious due to
- Date of hospitalisation

- Date of discharge
- Probable cause of death
- Date of death
- Autopsy performed
- Causality assessment in relation to Study procedure(s)
- Causality assessment in relation to Other medication
- Description of AE
- Narrative. In case a patient dies during the study, the investigator will summarise important information concerning the death in the eCRF

Intensity

The patients will be asked to assess the intensity of the reported AEs according to the following scale:

- Mild: awareness of sign or symptom, but easily tolerated
- Moderate: discomfort sufficient to cause interference with normal activities
- Severe: incapacitating, with inability to perform normal activities.

It is important to distinguish between serious and severe AEs. Severity is a measure of intensity whereas seriousness is defined by the criteria in Section 6.4.2. An AE of severe intensity need not necessarily be considered serious. For example, nausea that persists for several hours may be considered severe nausea, but not a SAE. On the other hand, a stroke that results in only a limited degree of disability may be considered a mild stroke but would be a SAE.

Concomitant medication

All changes in the patient's ordinary medication, eg, dose change, or addition of new medication must be reported in the MED module in the eCRF. Reasons for changes in medication, which reflect an AE, must be recorded on the AE form.

Causality collection

The Investigator will assess causal relationship between IP and each AE, and answer 'yes' or 'no' to the question 'Do you consider that there is a reasonable possibility that the event may have been caused by the investigational product?'

For SAEs causal relationship will also be assessed for other medication and study procedures. Note that for SAEs that could be associated with any study procedure the causal relationship is implied as 'yes'.

A guide to the interpretation of the causality question is found in Appendix B to the CSP.

Adverse Events based on signs and symptoms

All AEs spontaneously reported by the patient or care provider or reported in response to the open question from the study personnel: 'Have you had any health problems since the previous visit?', or revealed by observation will be collected and recorded in the eCRF. The question will be put to each patient in local language 24, 48, and 72 hours after start of the i.v. treatment, at the follow-up visit 30(+5) days after start of IP and at any unscheduled visit. When collecting AEs, the recording of diagnoses is preferred (when possible) to recording a list of signs and symptoms. However, if a diagnosis is known and there are other signs or symptoms that are not generally part of the diagnosis, the diagnosis and each sign or symptom will be recorded separately.

Adverse Events based on examinations and tests

The results from protocol mandated laboratory tests and vital signs will be summarised in the CSR. Deterioration as compared to baseline in protocol-mandated laboratory values, vital signs should therefore only be reported as AEs if they fulfil any of the SAE criteria or are the reason for discontinuation of treatment with the IP.

If deterioration in a laboratory value/vital sign is associated with clinical signs and symptoms, the sign or symptom will be reported as an AE and the associated laboratory result/vital sign will be considered as additional information. Wherever possible the reporting investigator uses the clinical, rather than the laboratory term (eg, anaemia versus low haemoglobin value). In the absence of clinical signs or symptoms, clinically relevant deteriorations in non-mandated parameters should be reported as AE(s).

Any new or aggravated clinically relevant abnormal medical finding at a physical examination as compared with the baseline assessment will be reported as an AE.

NB. Cases where a patient shows an AST **or** ALT ≥3xULN **or** total bilirubin ≥ 2xULN may need to be reported as SAEs, please refer to Appendix E 'Actions required in cases of combined increase of Aminotransferase and Total Bilirubin - Hy's Law', for further instructions.

Pregnancy

Should a pregnancy occur, it must be reported in accordance with the procedures described in Section 13.3.1, Procedures in case of pregnancy. Pregnancy in itself is not regarded as an AE unless there is a suspicion that an IP may have interfered with the effectiveness of a contraceptive medication.

6.4.4 Reporting of serious adverse events

All SAEs have to be reported, whether or not considered causally related to the IP, or to the study procedure(s). All SAEs will be recorded in the eCRF.

If any SAE occurs in the course of the study, then investigators or other site personnel inform appropriate AstraZeneca representatives immediately, or **no later than 24 hours** of when he or she becomes aware of it.

The designated AstraZeneca representative works with the investigator to ensure that all the necessary information is provided to the AstraZeneca Patient Safety data entry site **within one calendar day** of initial receipt for fatal and life threatening events **and within five calendar days** of initial receipt for all other SAEs.

For fatal or life-threatening AEs where important or relevant information is missing, active follow-up is undertaken immediately. Investigators or other site personnel inform AstraZeneca representatives of any follow-up information on a previously reported SAE immediately, or **no later than 24 hours** of when he or she becomes aware of it.

Once the Investigators or other site personnel indicate an AE is serious in the WBDC system, an automated email alert is sent to the designated AstraZeneca representative.

If the WBDC system is not available, then the Investigator or other study site personnel reports a SAE to the appropriate AstraZeneca representative by telephone, recognising that the same reporting time frames still apply. The AstraZeneca representative will advise the Investigator/study site personnel how to proceed. The investigator(s) is responsible for completing the eCRF as soon as the system becomes available again.

6.4.5 Laboratory safety assessment

At enrolment Hb, Hct, platelets, creatinine, APTT and PTC will be analysed locally (venous blood samples). Hb and Hct will also be analysed before start of i.v. treatment, every 8th hour during the 72 hours i.v. treatment, at the follow-up visit and at any unscheduled visits. Creatinine will also be analyses locally before start of i.v. treatment and 24 and 48 hours after start of i.v. treatment. The local creatinine value will be used to estimate GFR by using the MDRD formula (see Section 4.2), to assess whether patient is eligible for randomisation and to guide dosing of cimetidine.

In female patient with childbearing potential, a pregnancy test should be performed before randomisation, according to normal hospital routines.

A laboratory screening (central lab) will be done before and after i.v. treatment and at the follow-up visit on day 30(+5) and, if applicable, at any unscheduled visit. A laboratory screening will also be done in case of premature discontinuation from the study. See Section 5.9

Clinical (central) laboratory tests before i.v. treatment, after end of i.v. treatment, at the follow-up visit day 30(+5) and at any unscheduled visit will include:

Clinical chemistry:

- S-Creatinine
- S-Bilirubin, total
- S-Alkaline phosphatase (ALP)
- S-Aspartate aminotransferase (AST)
- S-Alanine aminotransferase (ALT)

Haematology:

- Hb
- B-White blood cell count (WBC)
- B-Platelets

In addition, a serology test for *H. pylori* will also be performed before the i.v. treatment.

Samples for clinical laboratory tests will be obtained by standardised techniques and assessed by a central laboratory for haematology and serum chemistry and *H. pylori* infection. Sample collection, labelling, storage and shipment will be described in a laboratory manual, which will be distributed by the central laboratory before the first patient is randomised. The samples may be taken in a patient whether he/she is fasting or not since the intra individual changes are the ones studied. The procedures used for individual patients should be kept constant.

The central and local laboratories will provide the investigator and AstraZeneca with test results including units, relevant reference ranges and updates as necessary. The result of local lab testing should be entered in the relevant eCRF.

The investigator must assess all laboratory results. If the measurements before i.v. treatment reveal any clinically relevant abnormal finding, incompatible with study participation as judged by the investigator, the patient should be discontinued from the study.

Calculated risk to individuals and community of the biological sample handling are expected to be none or very low as defined by the World Health Organisation (WHO). No blood samples will be taken from patient of high infective risk, as judged by the investigator.

NB. In case a patient shows an AST or ALT ≥3xULN or total bilirubin ≥ 2x ULN please refer to Appendix E. Actions required in cases of combined increase of Aminotransferase and Total Bilirubin – Hy's Law', for further instructions. Laboratory testing of such cases (Hy´s law

testing) is described in detail in the laboratory manual and results of such tests should be captured in the LIVERDI (Liver Diagnostic Investigations) module.

For blood volume see Section 7.1

6.4.6 Physical examination

A physical examination will be performed before i.v. treatment and at the follow-up visit at day 30(+5) or at any unscheduled visit, if applicable. The following organ systems will be examined according to normal hospital routines (results expressed as normal/abnormal) with specification:

- General appearance
- Cardiovascular
- Respiratory
- Abdomen
- Neurological system

6.4.7 ECG

6.4.7.1 Resting 12-lead ECG

A 12-lead ECG covering 5 (at least 3) sequential beats will be obtained after 5 minutes of supine rest before the i.v. treatment. The ECG will be evaluated by the investigator as "Normal" or "Abnormal" (and if "Abnormal" specified) in the eCRF. In case of an abnormal ECG, the investigator has to judge whether the patient is eligible to participate in the study or not, see exclusion criteria No.5 in Section 4.2. Signed and dated original and copy of ECG result should be stored with the medical records.

6.4.8 Vital signs

6.4.8.1 Pulse and blood pressure

Blood pressure and pulse rate will be measured after 5 minutes rest, before the i.v. treatment, every 8th hour during the 72 hours i.v. treatment and at the follow-up visit day 30(+5) and in case of study discontinuation.

Pulse (beats/min) will be measured over 30 seconds, in a supine position. Thereafter, systolic and diastolic BP (mmHg) will be measured using the same cuff size, appropriate for arm circumference, throughout the study.

6.4.9 Other safety assessments

Not applicable

6.5 Patient reported outcomes (PRO) (Not applicable)

6.6 Pharmacokinetics (Not applicable)

6.7 Pharmacogenetics (Not applicable)

6.8 Health economics (Not applicable)

7. BIOLOGICAL SAMPLING PROCEDURES

7.1 Volume of blood

The total volume of blood that will be drawn from each patient in this study is as follows:

Table 4 Volume of blood to be drawn from each patient

Assessment		Sample volume (ml)	No. of samples	Total volume (ml)
Exclusion criteria	APTT, PTC and platelets (local lab)	5	1	5
Exclusion criteria/IP dose adjustment	Creatinine (local lab)	10	3	30
Patient monitoring	Hb and Hct (local lab)	5	12	60
Safety (central lab)	Clinical chemistry	10	3	30
	Haematology	5	2	10
	H. pylori	2	1	2
Total				137

Note: Additional blood volume could be drawn in specific cases for safety reasons.

7.2 Handling, storage and destruction of biological samples

The routine safety blood samples will be used up or disposed of after analyses.

7.2.1 Pharmacokinetic and/or pharmacodynamic samples

Not applicable

7.2.2 Pharmacogenetic samples

Not applicable

7.3 Labelling and shipment of biohazard samples

The PI ensures that samples are labelled and shipped in accordance with the Laboratory Manual and the Biological Substance, Category B Regulations (materials containing or suspected to contain infectious substances that do not meet Category A criteria), see Appendix C 'IATA 6.2 Guidance Document'.

Any samples identified as Infectious Category A materials are not shipped and no further samples will be taken from the patient unless agreed with AstraZeneca and appropriate labelling, shipment and containment provisions are approved.

7.4 Chain of custody of biological samples

A full chain of custody is maintained for all samples throughout their lifecycle.

The PI at each centre keeps full traceability of collected biological samples from the patients while in storage at the centre until further shipment or disposal (where appropriate) and keeps documentation of receipt of arrival.

The sample receiver keeps full traceability of the samples while in storage and during use until used or disposed of or until further shipment and keeps documentation of receipt of arrival.

AstraZeneca keeps oversight of the entire life cycle through internal procedures, monitoring of study sites and auditing of external laboratory providers.

7.5 Withdrawal of informed consent for donated biological samples

If a patient withdraws consent to the use of donated biological samples, the samples will be disposed of/destroyed, and the action documented. If samples are already analysed, AstraZeneca is not obliged to destroy the results of this research.

As collection of the biological samples is not a critical part of the study, then the patient may continue in the study.

The PI:

- Ensures patients' withdrawal of informed consent to the use of donated samples is notified immediately to AstraZeneca
- Ensures that biological samples from that patient, if stored at the study site, are immediately identified, disposed of /destroyed, and the action documented
- Ensures the laboratory(ies) holding the samples is/are informed about the withdrawn consent immediately and that samples are disposed/destroyed, the action documented and the signed document returned to the study site
- Ensures that the patient and AstraZeneca are informed about the sample disposal.

AstraZeneca ensures the central laboratory(ies) holding the samples is/are informed about the withdrawn consent immediately and that samples are disposed of/destroyed and the action documented and returned to the study site.

8. ETHICAL AND REGULATORY REQUIREMENTS

8.1 Ethical conduct of the study

The study will be performed in accordance with ethical principles that have their origin in the Declaration of Helsinki and are consistent with International Conference on Harmonisation (ICH)/Good Clinical Practice (GCP), applicable regulatory requirements and the AstraZeneca policy on Bioethics and Human Biological Samples.

8.2 Patient data protection

The ICF will incorporate (or, in some cases, be accompanied by a separate document incorporating) wording that complies with relevant data protection and privacy legislation.

8.3 Ethics and regulatory review

An Ethics Committee (EC) should approve the final CSP, including the final version of the ICF and any other written information and/or materials to be provided to the patients. The investigator will ensure the distribution of these documents to the applicable EC, and to the study site staff.

The opinion of the EC should be given in writing. The investigator should submit the written approval to AstraZeneca before enrolment of any patient into the study.

The EC should approve all advertising used to recruit patients for the study.

AstraZeneca should approve any modifications to the ICF that are needed to meet local requirements. Before enrolment of any patient into the study, the final CSP, including the final version of the ICF, is approved by the national regulatory authority or a notification to the national regulatory authority is done, according to local regulations.

AstraZeneca will handle the distribution of any of these documents to the national regulatory authorities.

AstraZeneca will provide Regulatory Authorities, ECs and PIs with safety updates/reports according to local requirements, including Suspected Unexpected Serious Adverse Reactions (SUSARs), where relevant.

8.4 Informed consent

The PIs at each centre will:

- Ensure each patient is given full and adequate oral and written information about the nature, purpose, possible risk and benefit of the study
- Ensure each patient is notified that they are free to discontinue from the study at any time

- Ensure that each patient is given the opportunity to ask questions and allowed time to consider the information provided
- Ensure each patient provides signed and dated informed consent before conducting any procedure specifically for the study
- Ensure that patient "E-code" has been entered on the ICF after enrolling the patient into the study
- Ensure the original signed and dated original ICF(s) is/are stored in the Investigator's Study File
- Ensure a copy of the signed ICF is given to the patient
- Ensure that any incentives for patients who participate in the study as well as any provisions for patients harmed as a consequence of study participation are described in the ICF that is approved by an EC

The potential patient or his/her guardian/legal representative should sign ICF before any study-specific procedures are performed, which include the following:

- Withholding or discontinuing of any treatment
- Endoscopy including treatment and photo
- Collection of blood
- ECG
- Pregnancy test

Those patients who are unconscious or considered by the investigator clinically unable to consent at Screening and who are entered into the study by the consent of a legally acceptable representative should provide their own written informed consent for continuing to participate in the study as soon as possible on recovery, as applicable in accordance with local regulations.

8.5 Changes to the protocol and informed consent form

Study procedures will not be changed without the mutual agreement of the National Co-ordinating Investigator and the PI and AstraZeneca.

If there are any substantial changes to the CSP, then these changes will be documented in a CSP amendment and where required in a new version of the CSP (Revised CSP).

The amendment is to be approved by the relevant EC and if applicable, also the national regulatory authority approval, before implementation. Local requirements are to be followed for revised protocols.

AstraZeneca will distribute any subsequent amendments and new versions of the protocol to each PI(s) for distribution to EC see Section 8.3.

If a protocol amendment requires a change to a centre's ICF, AstraZeneca and the centre's EC are to approve the revised ICF before the revised form is used.

If local regulations require, any administrative change will be communicated to or approved by each EC.

8.6 Audits and inspections

Authorised representatives of AstraZeneca, a regulatory authority, or an EC may perform audits or inspections at the centre, including source data verification. The purpose of an audit or inspection is to systematically and independently examine all study-related activities and documents, to determine whether these activities were conducted, and data were recorded, analysed, and accurately reported according to the protocol,GCP, guidelines of the ICH, and any applicable regulatory requirements. The investigator will contact AstraZeneca immediately if contacted by a regulatory agency about an inspection at the centre.

9. STUDY MANAGEMENT BY ASTRAZENECA

9.1 Pre-study activities

Before the first patient is entered into the study, it is necessary for a representative of AstraZeneca to visit the investigational study site to:

- Determine the adequacy of the facilities
- Determine availability of appropriate patients for the study
- Discuss with the investigator(s) (and other personnel involved with the study) their responsibilities with regard to protocol adherence, and the responsibilities of AstraZeneca or its representatives. This will be documented in a Clinical Study Agreement between AstraZeneca and the investigator

9.2 Training of study site personnel

Before the first patient is entered into the study, an AstraZeneca representative will review and discuss the requirements of the CSP and related documents with the investigational staff and also train them in any study specific procedures and the WBDC and IWR/IVRS utilised.

The PI will ensure that appropriate training relevant to the study is given to all of these staff, and that any new information relevant to the performance of this study is forwarded to the staff involved.

The Principal Investigator will maintain a record of all individuals involved in the study (medical, nursing and other staff).

Before the first patient is enrolled for the study, the investigational staff will have an opportunity to discuss the study assessments, procedures associated with the collection of blood samples, with AstraZeneca personnel.

Consistency in the classification of PUB at endoscopy is crucial, and in order to obtain objective measurements, training material will be provided by AstraZeneca to harmonize the endoscopic assessments across study sites.

9.3 Monitoring of the study

To maintain blinding of the IP, during the study, both blinded and unblinded monitor will have regular contacts with study sites:

The blinded monitor will:

- Provide information and support to the investigator(s)
- Confirm that facilities remain acceptable
- Confirm that the investigational team is adhering to the protocol, that data are being accurately and timely recorded in the clinical chart and the eCRFs, including the data entry of and responses to queries issued and samples are handled in accordance with the Laboratory Manual
- Perform source data verification (a comparison of the data in the eCRFs with the patient's medical records at the hospital or practice, and other records relevant to the study), including verification of informed consent of participating patients. This will require direct access to all original records for each patient (e.g., clinic charts)

The unblinded monitor will verify IP accountability from receipt of IP through declaration of clean file and data base lock (see Section 5.7.1).

The AstraZeneca monitor will be available between visits if the investigator(s) or other staff at the centre needs information and advice about the study conduct.

9.3.1 Source data

Refer to the Clinical Study Agreement/applicable information for location of source data.

9.4 Study agreements

The PI at each/the centre should comply with all the terms, conditions, and obligations of the CSA, or equivalent, for this study. In the event of any inconsistency between this CSP and the CSA, the terms of CSP shall prevail with respect to the conduct of the study and the treatment of patients and in all other respects, not relating to study conduct or treatment of patients, the terms of the CSA shall prevail.

Agreements between AstraZeneca and the PI should be in place before any study-related procedures can take place, or patients are enrolled.

9.4.1 Archiving of study documents

The investigator follows the principles outlined in the CSA.

9.5 Study timetable and end of study

The end of the study is defined as Last patient last visit.

The study is expected to start in and to end by .

Enrolment will be stopped when 200 evaluable patients have been randomised.

The study may be terminated at individual centres if the study procedures are not being performed according to GCP, or if recruitment is slow. AstraZeneca may also terminate the entire study prematurely if concerns for safety arise within this study or in any other study with esomeprazole. The rate of inclusion at the different sites will be encouraged and evaluated on a regular basis.

The planned overall timetable for the study is as follows:

First patient in

Last patient in

Last patient last visit

Database lock

10. DATA MANAGEMENT BY ASTRAZENECA OR DELEGATE

Data management will be performed by the AstraZeneca Data Management Centre (DMC).

The data collected through third party sources will be obtained and reconciled against study data.

AE and medical/surgical history will be classified according to the terminology of the latest version the Medical Dictionary for Regulatory Activities (MedDRA). Medications will be classified according to the AstraZeneca Drug Dictionary. All coding will be performed by the Medical Coding Team at the AstraZeneca DMC.

Data queries will be raised for inconsistent, impossible or missing data. All entries to the study database will be available in an audit trail.

The data will be validated as defined in the Data Management Plan (DMP). Quality control procedures will be applied to each stage of data handling to ensure that all data are reliable and have been processed correctly.

When all data have been coded, validated, signed and locked, clean file will be declared. Any treatment revealing data may thereafter be added and the final database will be locked.

Data associated with biological samples will be transferred to laboratories internal or external to AstraZeneca.

11. EVALUATION AND CALCULATION OF VARIABLES BY ASTRAZENECA

11.1 Calculation or derivation of efficacy variable(s)

11.1.1 Derivation or calculation of rebleeding variable

Rebleeding within 72 hours, 7 days and 30 days will be calculated from the date and time for significant rebleeding, as recorded in the eCRF.

11.1.2 Derivation or calculation of endoscopic re-treatment variable

Endoscopic re-treatment within 72 hours and 30 days will be calculated from the date and time for start of endoscopic re-treatment as recorded in the eCRF.

11.1.3 Derivation or calculation of surgery variable

Surgery within 72 hours and 30 days that is caused by rebleeding will be calculated from the date and time for start of such surgery as recorded in the eCRF.

11.1.4 Derivation or calculation of transfusion variable

The total amount of blood transfusions within 72 hours and 30 days will be calculated from the date, time and amount of blood transfusions as recorded in the eCRF.

11.2 Calculation or derivation of safety variable(s)

11.2.1 Other significant adverse events (OAE)

During the evaluation of the AE data, an AstraZeneca medically qualified expert will review the list of AEs that were not reported as SAEs and Discontinuation of IP due to adverse

event(s) (DAEs). Based on the expert's judgement, significant AE of particular clinical importance may, after consultation with the Global Patient Safety Physician, be considered OAEs and reported as such in the CSR. A similar review of laboratory/vital signs data will be performed for identification of OAEs.

Examples of these are marked haematological and other laboratory abnormalities, and certain events that lead to intervention (other than those already classified as serious), dose reduction or significant additional treatment.

11.3 Calculation or derivation of patient reported outcome variables (Not applicable)

11.4 Calculation or derivation of pharmacokinetic variables (Not applicable)

11.5 Calculation or derivation of pharmacodynamic variables (Not applicable)

11.6 Calculation or derivation of pharmacogenetic variables (Not applicable)

11.7 Calculation or derivation of health economic variables (Not applicable)

12. STATISTICAL METHODS AND SAMPLE SIZE DETERMINATION

12.1 Description of analysis sets

12.1.1 Efficacy analysis set (Full Analysis Set)

All randomised patients, who started the randomised i.v. treatment (bolus dose), will be included in the FAS. The FAS data will be analysed as randomised, ie, patients are analysed based on their randomised treatment. Randomised treatment is defined as the treatment associated with the randomisation code given to the patient, identified via the randomisation schedule. The FAS will be used in the analysis of the primary objective and all other efficacy analyses.

12.1.2 Safety analysis set

All patients who received at least one dose of IP and for whom any post-dose data are available will be included in the safety population. Throughout the safety results sections, erroneously treated patients (eg, those randomised to treatment A but actually given treatment B) will be accounted for in the actual treatment group.

12.2 Methods of statistical analyses

The efficacy variable, rebleeding within 72 hours, will be presented using descriptive statistics by treatment group, baseline Forrest class and type of endoscopic treatment. Rebleeding events for the other time points, need for endoscopic re-treatments or surgery due to rebleeding, and number of blood units transfused will be handled in a similar fashion.

The rebleeding variable will also be analysed descriptively in subgroups based on age (up to or above 65 years) and gender.

Patients who leave the study prematurely without having had rebleeding will be included in the analysis and considered to have had no rebleeding.

Safety variables for the two groups will be presented using descriptive statistics.

12.2.1 Interim analyses

No interim analysis will be performed.

12.3 Determination of sample size

One hundred patients per treatment group are considered appropriate to generate safety and tolerability data in China, which is an important objective for this study. This study is not powered to allow formal statistical testing of efficacy. Descriptive data of the rate of rebleeding after endoscopic haemostatic treatment will be presented.

12.4 Data monitoring committee

There will be no independent unblinded Data Safety Monitoring Board in this study. An internal safety team (consisting of study physician, patient safety specialist, and study leader) will review blinded safety data such as SAEs, DAEs, AEs and rebleedings on a regular basis throughout the study.

13. IMPORTANT MEDICAL PROCEDURES TO BE FOLLOWED BY THE INVESTIGATOR

13.1 Medical emergencies and AstraZeneca contacts

The PI is responsible for ensuring that procedures and expertise are available to handle medical emergencies during the study. **A medical emergency usually constitutes an SAE and is to be reported as such, see Section 6.4.4**

In the case of a medical emergency the investigator may contact the Study Leader. If the Study Leader is not available, contact the Study Physician/other physician at the AstraZeneca Research and Development.

Table 5 Medical Emergency and AstraZeneca Contact Information

Name	Role in the study	Address & telephone number
	Study Leader	
	Study Physician	

The local AstraZeneca representative could be found in the "Supplement 2, Study Team Contacts in the Event of Emergency Situations, Overdose or Pregnancy".

Study Physician

13.2 Overdose

The symptoms described in connection with deliberate oral esomeprazole overdose (limited experience of doses in excess of 240 mg/day) are transient. Single oral doses of 80 mg and i.v. doses of 100 mg esomeprazole were uneventful. No specific antidote is known. Esomeprazole is extensively plasma protein bound and is therefore not readily dialyzable. As in any case of overdose, treatment should be symptomatic and general supportive measures should be utilised.

Clinical features of overdoses of cimetidine include reports of severe central nervous system (CNS) symptoms, such as unresponsiveness, following ingestion of between 20g and 40g of

cimetidine. There have been deaths in adults who were reported to have ingested over 40g of cimetidine orally as a single dose. In animal toxicity experiments CNS depression, hypotension, tachycardia, liver enzyme elevation and renal abnormalities have been observed. In case of overdose of i.v. cimetidine supportive therapy and careful monitoring for evolving clinical symptoms should be initiated. In severe cases mechanical ventilation may be needed.

All information on study drug exposure is to be collected in the dose module in the eCRF and AEs is recorded on the relevant AE modules in the eCRF, for information regarding recording AEs and reporting of SAEs see Section 6.4.3 and 6.4.4 respectively.

13.3 Pregnancy

All outcomes of pregnancy should be reported to AstraZeneca.

13.3.1 Maternal exposure

Pregnant women, as well as those who are planning pregnancy or are breast-feeding, are excluded from the study. In addition, fertile women not using acceptable contraceptive measures, as judged by the investigator, should not be included in the study. Clinical experience with esomeprazole in pregnant women is limited and patients that become pregnant must be discontinued from the study.

If a patient becomes pregnant during the course of the study, IP should be discontinued immediately.

Pregnancy itself is not regarded as an AE unless there is a suspicion that the IP under study may have interfered with the effectiveness of a contraceptive medication. Congenital abnormalities/birth defects and spontaneous miscarriages should be reported and handled as SAEs. Elective abortions without complications should not be handled as AEs. The outcome of all pregnancies (spontaneous miscarriage, elective termination, ectopic pregnancy, normal birth or congenital abnormality) should be followed up and documented even if the patient was discontinued from the study.

If any pregnancy occurs in the course of the study, then investigators or other site personnel inform appropriate AstraZeneca representatives immediately, or **no later than 24 hours** of when he or she becomes aware of it.

The designated AstraZeneca representative works with the investigator to ensure that all relevant information is provided to the AstraZeneca Patient Safety data entry site within 1 or 5 days for SAEs, see Section 6.4.4 and within 30 days for all other pregnancies.

The same timelines apply when outcome information is available.

The PREGREP module in the eCRF is used to report the pregnancy and the PREGOUT is used to report the outcome of the pregnancy.

13.3.2 Paternal exposure

No risk from paternal exposure has been identified or suspected from the considerable experience of esomeprazole during market use and the clinical study programs. Thus, no specific precautions or actions regarding paternal exposure are considered to be required.

14. LIST OF REFERENCES

AZ study D9615C00015
An open, randomised, five-way crossover study of esomeprazole given as short-term intravenous infusions of 40, 80 and 120 mg followed by a continuous infusion of 8 or 4 mg/h regarding effect on 24-hour intragastric pH and pharmacokinetics in healthy patients.9 June, 2004 [data on file].

AZ study D9615L00007
An open, randomised, five-way cross over study to assess the pharmacokinetics, pharmacodynamics and safety of esomeprazole given as intravenous infusion /injection in healthy Chinese subjects [data on file].

AZ study D961DL00004
A randomised, double-blind, double-dummy, parallel-group, activecontrolled, multicenter study to assess the efficacy and safety of esomeprazole 40 mg q12h i.v. or omeprazole 40 mg q12h i.v. administration for 5 days in patients with acute non-variceal upper gastrointestina bleeding [data on file].

AZ study NIS-GCN-DUM- 2010/1
A Survey on Peptic Ulcer Bleeding in China [data on file].

Barkun et al 2010
Barkun AN, Bardou M, Kuipers EJ, Sung J, Hunt RH, Martel M, Sinclair P. International Consensus Upper Gastrointestinal Bleeding Conference Group.International consensus recommendations on the management of patients with nonvariceal upper gastrointestinal bleeding. Ann Intern Med. 2010 Jan 19;152(2):101-13.

Blatchford et al 1997
Blatchford O, Davidson LA, Murray WR, Blatchford M, Pell J. Acute upper gastrointestinal haemorrhage in west of Scotland: case ascertainment study. BMJ. 1997 Aug 30;315(7107):510-4.

Forrest et al 1974
Forrest J.A, Finlayson N.D et al. Endoscopy in gastrointestinal bleeding. Lancet 1974; 2(7877):394-7.

Green et al 1978
Green FW, Jr., Kaplan MM, Curtis LE and Levine PH. Effect of acid and pepsin on blood coagulation and platelet aggregation. A possible contributor prolonged gastroduodenal mucosal hemorrhage. Gastroenterology 1978;74(1):38-43.

Hasselgren et al 1997
Hasselgren G, Lind T, Lundell L, Aadland E, Efskind P, Falk A, et al. Continuous intravenous infusion of omeprazole in elderly patients with peptic ulcer bleeding. Results of a placebo-controlled multicenter study. Scand J Gastroenterol 1997;32(4):328-33.

Holster and Kuipers 2011
Holster IL, Kuipers EJ. Update on the Endoscopic Management of Peptic Ulcer Bleeding. Curr Gastroenterol Rep 2011;13:525–531.

Khuroo et al 1997
Khuroo MS, Yattoo GN, Javid G, Khan BA, Shah AA, Gulzar GM, et al. A comparison of omeprazole and placebo for bleeding peptic ulcer. N Engl J Med 1997;336(15):1054-8.

Kupfer et al 2000
Kupfer Y, Cappell MS, Tessler S. Acute gastrointestinal bleeding in the intensive care unit; The intensivist's perspective. Gastroenterol Clin North Am 2000; 29(2):275-307.

Laine and Peterson 1994
Laine L, Peterson WL. Bleeding peptic ulcer. N Engl J Med 1994;331:717-727.

Laine et al 2010
Laine L, Spiegel B, Rostom A, Moayyedi P, Kuipers EJ, Bardou M, et al. Methodology for Randomized Trials of Patients With Nonvariceal Upper Gastrointestinal Bleeding: Recommendations From an International Consensus Conference. Am J Gastroenterol 2010; 105:540–550.

Laine 2012
Laine L, Jensen DM. Management of Patients With Ulcer Bleeding. Am J Gastroenterol 2012;107:345–360.

Lau et al 1998
Lau JY, Chung SC, Leung JW, Lo KK, Yung MY, Li AK. The evolution of stigmata of hemorrhage in bleeding peptic ulcers: a sequential endoscopic study. Endoscopy 1998;30:513 -8.

Lau et al 2000
Lau JY, Sung JJ, Lee KK, Yung MY, Wong SK, Wu JC, et al. Effect of intravenous omeprazole on recurrent bleeding after endoscopic treatment of bleeding peptic ulcers. N Engl J Med 2000;343(5):310-6.

Leontiadis et al 2005
Leontiadis GI, Sharma, VK, Howden, CW. Systematic review and meta-analysis: enhanced efficacy of proton-pump inhibitor therapy for peptic ulcer bleeding in Asia--a post hoc analysis from the Cochrane Collaboration. Aliment Pharmacol Ther 2005b;21:1055-61.

Leontiadis et al 2006
Leontiadis GI, Sharma VK, Howden CW. Proton pump inhibitor treatment for acute peptic ulcer bleeding. Cochrane Database Syst Rev. 2006 Jan 25;(1):CD002094.

Li et al 2000
Li Y, Sha W, Nie Y, Wu H, She Q, Dai S, et al. Effect of intragastric pH on control of peptic ulcer bleeding. J Gastroenterol Hepatol 2000;15(2):148-54.

Miner et al 2003
Miner P, Jr., Katz PO, Chen Y and Sostek M. Gastric acid control with esomeprazole, lansoprazole, omeprazole, pantoprazole, and rabeprazole: a five-way crossover study. Am J Gastroenterol 2003;98(12):2616-20.

Miner et al 2006
Miner P, Katz PO, Chen Y, Sostek M. Reanalysis of intragastric pH results based on updated correction factors for Slimline and Zinetics 24 single-use pH catheters. Am J Gastroenterol 2006;101:404-405.

Patchett et al 1989
Patchett SE, Enright H, Afdhal N, O'Connell W and O'Donoghue DP. Clot lysis by gastric juice: an in vitro study. Gut 1989;30(12):1704-7.

Rockall et al 1996
Rockall TA, Logan RFA, Devlin HB, Northfield T C, and the steering committee and members of the National Audit of Acute Upper Gastrointestinal Haemorrhage. Risk assessment after acute upper gastrointestinal Haemorrhage. Gut 1996; 38: 316-321.

Röhss et al 2004
Röhss K, Wilder Smith C, Jansson L, Nauclér E. Esomeprazole 20mg provides more effective intragastric acid control than maintenance dose rabeprazole, lansoprazole or pantoprazole in healthy volunteers. Clin Drug Invest 2004; 24(1):1–7.

Schaffalitzky de Muckadell et al 1997
Schaffalitzky de Muckadell OB, Havelund T, Harling H, Boesby S, Snel P, Vreeburg EM, et al. Effect of omeprazole on the outcome of endoscopically treated bleeding peptic ulcers. Randomized double-blind placebo-controlled multicentre study. Scand J Gastroenterol 1997;32(4):320-7.

Schiller et al 2002
Schiller KFR, Cockel R, Hunt RH, Warren BF. Atlas of gastrointestinal endoscopy and related pathology, 2nd edn. Oxford: Blackwell Science; 2002. p.95-97.

Somberg et al 2008
Somberg L, Morris Jr. J, Fantus R, Graepel J, Field BG, Lynn, R, et al. Intermittent Intravenous Pantoprazole and Continuous Cimetidine Infusion: Effect on Gastric pH Control in Critically Ill Patients at Risk of Developing Stress-Related Mucosal Disease. J Trauma. 2008;64:1202–1210.

Speechler 2002
Speechler SJ. Peptic ulcer disease and its complications. In Feldman M, Friedman LS, Sleisenger MH, eds. Sleisenger & Fordtran's Gastrointestinal and Liver Disease, 7th Edn. Philadelphia, PA: WB Saunders Company; 2002. p.747-781.

Spiro 1993
Spiro HM. Clinical Gastroenterology 4th edn. New York, NY: McGraw-Hill Inc; 1993. p.251-281.

Sung et al 2009
Sung JYY, Barkun A, Kuipers EJ, Mössner J, Jensen DM, Stuart R, et al. Intravenous Esomeprazole for Prevention of Recurrent Peptic Ulcer Bleeding. A Randomized Trial. Ann Intern Med. 2009;150:455-464.

Sung et al 2011
Sung JJY, Chan FKL, Chen M, Ching JYL, 3 K Y Ho, Kachintorn U et al. Asia-Pacific Working Group consensus on non-variceal upper gastrointestinal bleeding. Gut 2011;60:1170-1177. doi:10.1136/gut.2010.230292

van Leerdam et al 2003
van Leerdam ME, Vreeburg EM, Rauws EA, Geraedts AA, Tijssen JG, Reitsma JB, et al. Acute upper GI bleeding: did anything change? Time trend analysis of incidence and outcome of acute upper GI bleeding between 1993/1994 and 2000. Am J Gastroenterol 2003;98(7):1494-9.