AstraZeneca

Drug product:	Esomeprazole	**SYNOPSIS**	
Drug substance(s):	Esomeprazole		
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A Randomised, Double-Blind, Placebo Controlled Explorative Study to Investigate the Efficacy and Safety of Esomeprazole in the Prevention of Post Operative Nausea and Vomiting

Study centre(s)

This study was conducted in 23 centres in Norway (14 centres) and Sweden (9 centres).

Publications

None at the time of writing this report.

Study dates		**Phase of development**
First subject enrolled	14 March 2004	Therapeutic exploratory (II)
Last subject completed	12 October 2004	

Objectives

- Primary Objective:
  - To investigate the efficacy of esomeprazole in preventing the occurrence of postoperative nausea and vomiting (PONV).
- Secondary Objectives:
  - To investigate the efficacy of esomeprazole on the symptoms of nausea, retching and vomiting as measured by the Rhodes Index of Nausea, Vomiting and Retching (INVR) questionnaire and on nausea as measured by a 100 mm Visual Analogue Scale (VAS).

- To investigate the efficacy of esomeprazole in increasing the proportion of subjects with absence of vomiting as well as in reducing the amount (measured as weight) of postoperative vomiting during the first 24hours (h) postoperatively.

- To investigate the efficacy of esomeprazole in increasing the proportion of subjects with absence of nausea as well as in reducing the duration and severity of postoperative nausea during the first 24h postoperatively.

- To investigate the efficacy of esomeprazole in increasing the proportion of subjects with absence of retching or vomiting as well as in reducing the frequency and severity of postoperative retching or vomiting during the first 24h postoperatively.

- To compare the length-of-stay in the PACU between the two groups.

- To investigate the efficacy of esomeprazole in reducing the need for anti-emetic rescue medication as described by the proportion of subjects requiring anti-emetic rescue medication, time to first administration of anti-emetic rescue medication and total amount required during the first 24h postoperatively.

- To evaluate the safety and tolerability of esomeprazole and placebo.

Study design

This was a randomised, double-blind, parallel-group, multicentre study comparing the efficacy and safety of esomeprazole and placebo in the prevention of PONV, when given to subjects undergoing elective surgery.

Target subject population and sample size

The study population comprised male and female subjects who were classified according to the American Society of Anaesthesiologists (ASA) Classification System as physical status 1 or 2, were between the ages of 18-70 years and were scheduled for elective laparoscopic or open gynaecological surgery or laparoscopic cholecystectomy, with a preoperative predicted Apfel Score of 3-4, which corresponds to a risk of PONV>50%.

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

Esomeprazole capsules or matching placebo and esomeprazole powder for solution for injection/infusion or matching placebo. Ondansetron 4mg (2ml), given according to label, was used as anti-emetic rescue medication.

Duration of treatment

Approximately 24 - 28h, dependant on the interval between the first and second dose of study medication (the timing of the second dose depended on the time for start of surgery).

Criteria for evaluation (main variables)

Efficacy

- **Primary variable:**
  - Complete absence of PONV during 24h postoperatively, including no need for anti-emetic rescue medication, as reported by the study personnel.
- **Secondary variables:**
  - Complete absence of nausea /retching/vomiting, including no need for anti-emetic rescue medication during 24h postoperatively.
  - Amount of vomit (measured in weight) during 24h postoperatively.
  - Duration and severity nausea during 24h postoperatively.
  - Frequency and severity of retching or vomiting during 24h postoperatively.
  - Time to first administration of anti-emetic rescue medication.
  - Proportion of subjects requiring anti-emetic rescue medication during 24h postoperatively.
  - Total amount of anti-emetic rescue medication required during 24h post-operatively.
- **Patient reported outcomes (PROs)**
  - Nausea, retching and vomiting during 24h postoperatively, measured by the Rhodes (INVR) questionnaire.
  - Nausea, during 24h postoperatively, measured by a 100 mm VAS.
- **Health economics**
  - Time from end of surgery to discharge readiness (assessed by the Aldrete score) from the PACU.
- **Safety**
  - The incidence, severity and type of adverse events.
  - The incidence of clinically important changes in laboratory values, heart rate (HR) and blood pressure (BP), electrocardiogram (ECG) and SaO2.
- **Genetics (Not applicable)**

Statistical methods

The primary variable, ie, complete absence of PONV during 24h postoperatively, was analysed both for an intention-to-treat (ITT) population and for a per protocol (PP) population. The secondary variables were analysed for the ITT population only. The safety population was used for evaluating the safety variables.

The proportion of subjects with complete absence of PONV in each treatment group and the difference in the proportion of subjects with complete absence of PONV between esomeprazole and placebo were evaluated with two-sided 95% confidence intervals (CI) and a Cochran-Mantel-Haenzel (CMH) test stratified on type of operation.

Subject population

The demographic characteristics of the study population is described in Table S 1.

Table S 1 Subject population and disposition

		Esomeprazole		Placebo		Total	
Population							
N randomised (N planned)		151	(155)	154	(155)	305	(310)
Demographic characteristics							
Sex (n and % of subjects)	Male	2	(1%)	7	(5%)	9	(3%)
	Female	139	(99%)	136	(95%)	275	(97%)
Age (years)	Mean (SD)	46.8	(10.1)	44.2	(11.7)	45.5	(11.0)
	Range	19 to 71		19 to 69		19 to 71	
Race (n and % of subjects)	Caucasian	140	(99%)	143	(100%)	283	(100%)
	Oriental	1	(1%)	0	(0%)	1	(0%)
Baseline characteristics							
Apfel score	3	92	(65%)	90	(63%)	182	(64%)
	4	49	(35%)	53	(37%)	102	(36%)
Surgical procedure	Laparoscopic gynaecological surgery	26	(18%)	25	(17%)		(18%)
	Open gynaecological surgery	39	(28%)	35	(24%)		(26%)
	Laparoscopic cholecystectomy	76	(54%)	83	(58%)		(56%)
Disposition							
N (%) of subjects who	Completed	141	(93)	142	(92%)	283	(93%)
	discontinued	10	(7%)	12	(8%)	22	(7%)

	Esomeprazole	Placebo	Total
N analysed for safety[a]	150	152	302
N analysed for efficacy (ITT)	141	143	284
N analysed for efficacy (PP)	128	123	251

[a] Number of subjects who took at least 1 dose of study treatment and had at least 1 data point after dosing
ITT=Intention-to-treat; N=Number; PP=Per-protocol

The proportion of subjects who had important protocol deviations leading to exclusion from the PP analysis was generally similar across treatment groups. Overall, the treatment groups were comparable in terms of demographic characteristics and baseline values.

Efficacy results

The cumulative proportion of subjects with complete absence of PONV 24h postoperatively, including no need for anti-emetic rescue medication, is presented for the ITT population in Table S 2.

Primary variable:

Table S 2 Cumulative proportion of subjects with complete absence of PONV after 2, 6, 12, 18 and 24 hours and CMH test stratified for type of surgery, ITT population

	Type of surgery	Esomeprazole (n=141)	Placebo (n=143)
2 hours	Laparoscopic surgery	59/102 (59.0%)	56/108 (52.3%)
	Open surgery	15/39 (38.5%)	21/35 (60.0%)
	Total	74/141 (53.2%)	77/143 (54.2%)
6 hours	Laparoscopic surgery	34/102 (33.3%)	29/108 (27.1%)
	Open surgery	9/39 (23.1%)	11/35 (31.4%)
	Total	43/141 (30.5%)	40/143 (28.2%)
12 hours	Laparoscopic surgery	28/102 (27.5%)	24/108 (22.4%)
	Open surgery	6/39 (15.4%)	6/35 (17.1%)
	Total	34/141 (24.1%)	30/143 (21.1%)
18 hours	Laparoscopic surgery	28/102 (27.5%)	23/108 (21.5%)
	Open surgery	6/39 (15.4%)	6/35 (17.1%)
	Total	34/141 (24.1%)	29/143 (20.4%)
24 hours	Laparoscopic surgery	28/102 (27.5%)	23/108 (21.3%)
	Open surgery	5/39 (12.8%)	4/35 (11.4%)
	Total	33/141 (23.4%)	27/143 (18.9%)
	CMH test p-value	0.3080	

Esomeprazole had no statistically significant effect on the occurrence of PONV, including need for anti-emetic rescue medication, during 24h postoperatively.

Secondary variables:

The proportion of patients with absence of vomiting was reduced from 37% to 24% after esomeprazole, and the mean amount of vomit was reduced to less than half compared to placebo-treated patients. The mean scores for vomiting (occurrence and experience) in the Rhodes (INVR) questionnaire from 0 to 24h postoperatively were significantly lower in patients treated with esomeprazole, whereas the mean scores for retching (occurrence and experience) were lower in placebo-treated patients from 0 to 6h postoperatively. For all other secondary variables, no differences were observed between the two groups.

Safety results

The frequency of AEs was similar between the oral treatment groups as well as between the IV treatment groups. No patients died during the study. Four SAEs were reported, 2 in the esomeprazole IV group and 2 in the placebo IV group. One AE in the IV placebo group led to discontinuation of study treatment. No events were classified as other significant adverse event (OAE).

A mean decrease in the haemoglobin values between the baseline and last visit was seen in the esomeprazole group and in the placebo group.An increase in the values of ALAT and ASAT between the baseline and last visit was seen for both treatment groups.The changes can be seen as a reflection of the surgical intervention conducted on the previous day.

Esomeprazole in doses of 40mg oral single administration followed by 40mg IV bid in this clinical setting was well tolerated.

Table S 3 Number (%) of subjects who had at least 1 adverse event in any category and total numbers of adverse events (safety population)

Category of adverse events[a]	Esomeprazole 40mg oral (n=150)		Esomeprazole 40mg IV bid (n=147)		Placebo oral (n=152)		Placebo IV bid (n=150)	
Any adverse events	2	(1.3)	38	(25.9)	1	(0.7)	38	(25.3)
Serious Aes	0		2	(1.4)	0		2	(1.3)
Serious AEs leading to death	0		0		0		0	
Serious AEs not leading to death	0		2	(1.4)	0		2	(1.3)
Discontinuation of study treatment due to Aes	0		0		0		1	(0.7)
Other significant Aes	0		0		0		0	
Related AEs[b]	0		3	(2.0)	0		1	(0.7)
Severe Aes	0		2	(1.4)	0		3	(2.0)

[a] Subjects with multiple events in the same category are counted only once in that category.
Subjects with events in more than 1 category are counted once in each of those categories.
[b] Related AEs are those for which there was a possible relationship to investigational product as judged by the investigator.
Data derived from Appendix 12.2.7.The number of subjects may differ from Section 6 as only discontinuation of study treatment due to an AE is listed in this table.

Table S 4 Number (%) of subjects with the most commonly reported adverse events, sorted by the esomeprazole groups, presented by preferred term (safety population)

Preferred term	Esomeprazole 40 oral (n=150)		Esomeprazole 40mg IV bid (n=147)		Placebo oral (n=152)	Placebo IV bid (n=150)	
Hypotension	0		6	(4.1)	0	10	(6.7)
Bradycardia	0		5	(3.4)	0	4	(2.7)
Headache	1	(0.7)	3	(2.0)	0	2	(1.3)
Anxiety	0		3	(2.0)	0	1	(0.7)
Operative haemorrhage	0		3	(2.0)	0	0	
Pruritus	0		3	(2.0)	0	0	
Arthralgia	0		2	(1.4)	0	0	
Bladder perforation	0		2	(1.4)	0	0	
Dizziness	0		2	(1.4)	0	1	(0.7)
Urinary retention	0		0		0	4	(2.7)

Included in this table are AEs reported for at least 2 patients.