AstraZeneca

Post-marketing Clinical Study Report

Drug substances	omeprazole, amoxicillin, clarithromycin
Edition	Version 1.0
Study code No.	GOM3541
Date	9 December 2004

A multicentre, randomised, double-blind, parallel study to investigate the efficacy and safety of *Helicobacter pylori* eradication one-week therapy with triple combination of Omeprazole, Amoxicillin and Clarithromycin in Japanese peptic ulcer patients (Phase IV post-marketing clinical study)

Study dates:	First subject enrolled:	7 May 2003
	Last subject completed:	1 April 2004
Phase of development:	Therapeutic use (IV)	

This study was performed in compliance with Good Post-Marketing Surveillance Practice and Good Clinical Practice

Drug substance(s)	omeprazole, amoxicillin, clarithromycin	**SYNOPSIS**	
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A multicentre, randomised, double-blind, parallel study to investigate the efficacy and safety of *Helicobacter pylori* eradication one-week therapy with triple combination of Omeprazole, Amoxicillin and Clarithromycin in Japanese peptic ulcer patients (Phase IV post-marketing clinical study)

Study centre(s)

This study was conducted at 14 centres in Japan including Internal Medicine, Nakano Sun-bright Clinic.

Publications

None at the time of writing this report

Study dates		**Phase of development**
First subject enrolled	7 May 2003	Therapeutic use (IV)
Last subject completed	1 April 2004	

Objectives

Primary objective

To investigate the efficacy of the triple therapy with omeprazole (OPZ) 40 mg/day, amoxicillin (AMPC) 1500 mg/day, and clarithromycin (CAM) 400 mg/day or 800 mg/day for Helicobacter pylori (H. pylori) -positive patients with peptic ulcer by assessment of H. pylori eradication rate.

Secondary objectives

Secondary objectives are the following.

- To evaluate *H. pylori* eradication rates by treatment group for gastric ulcer and duodenal ulcer
- To evaluate *H. pylori* eradication rates by genotype of CYP2C19 (Homo-EM/ Hetero-EM/PM) for each treatment group
- To evaluate *H. pylori* eradication rates by susceptibility to AMPC and CAM (AMPC: susceptible/non-susceptible, CAM: susceptible/intermediate/resistant) at pre-treatment for each treatment group
- To evaluate rates of development of resistance to AMPC and CAM (AMPC: from susceptible at pre-treatment to non-susceptible at post-treatment, CAM: from susceptible at pre-treatment to intermediate or resistant at post-treatment) in subjects with failed eradication for each treatment group
- To investigate the safety by assessment of the adverse events

Study design

This study was a multicentre, randomised, double-blind, parallel study to investigate the efficacy and safety of *Helicobacter pylori* eradication after one-week therapy with triple combination of Omeprazole, Amoxicillin and Clarithromycin in Japanese peptic ulcer patients.

Target subject population and sample size

The subjects were those who met all the following inclusion criteria.

(1) Provision of written informed consent

(2) Provision of consent to genotyping test

(3) Subjects whose ulcer stage was classified into either S_1 or S_2 according to the Sakita & Miwa Classification. In case the subject had both gastric ulcer and duodenal ulcer and each of those met the above ulcer stage criteria, the subject would be enrolled as either gastric ulcer or duodenal ulcer, being categorised based on the following prioritisation order.
1) The ulcer which occurred most recently in the subject's medical history (the ulcer which endoscopically diagnosed most recently) (the ulcer which was subjected to the investigation of the subject data).
2) The ulcer of which the ulcer stage was S_1.
3) The ulcer which was considered to be more intractable, e.g. having many ulcer lesions.

(4) Subjects who were proven to be *H. pylori* positive by both rapid urease test and culture

(5) Subjects aged 20 years or older (including those aged 20)

The number of subjects were planned to be 130 each for Low and High dose groups (65 gastric ulcer patients and 65 duodenal ulcer patients per group), totalling to 260 subjects.

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

Investigational product

OPZ 20 mg tablet, AMPC 250 mg capsule, CAM 200 mg tablet and CAM placebo tablet

Dosage

Low dose group: OPZ 20 mg, AMPC 750 mg and CAM 200 mg (twice daily)

High dose group: OPZ 20 mg, AMPC 750 mg and CAM 400 mg (twice daily)

Investigational product code

OAC-003

Lot Number

3541

Duration of treatment

One week for the eradication therapy period (treatment period) and 6 weeks for the observation period.

Criteria for evaluation (main variables)

Efficacy

Primary outcome variable

H. pylori eradication rate

Secondary outcome variables

- *H. pylori* eradication rates by treatment group for gastric ulcer and duodenal ulcer
- *H. pylori* eradication rates by genotype of CYP2C19 (Homo-EM, Hetero-EM, PM) for each treatment group
- *H. pylori* eradication rates by susceptibility to AMPC and CAM (AMPC: susceptible/non-susceptible, CAM: susceptible/intermediate/resistant) at pre-treatment for each treatment group
- Rates of development of resistance to AMPC and CAM (AMPC: susceptible at pre-treatment to non-susceptible at post-treatment, CAM: susceptible at pre-treatment to

intermediate/resistant at post-treatment) in subjects with failed eradication for each treatment group

Safety

Primary outcome variable

None

Secondary outcome variable

Adverse events

Statistical methods

H. pylori eradication rate (negative rate in *H. pylori* status at 6 weeks after completion of dosing) was calculated by group together with 90 % CI (both sides).

For the adverse events observed after start of administration of investigational product (eradication therapy period and observation period), incidence of AEs, incidence of SAEs, percentage of discontinuation due to AEs, and incidence of such AEs as diarrhoea and loose stool were calculated with two-sided 90% CI by treatment group and by eradication therapy period/observation period.

Subject population

Disposition of the subjects in this study is shown in Figure S 1. A total of 335 subjects were screened, of which, 288 subjects (143 subjects in Low dose group and 145 in High dose group) were randomised to the investigational product. Of those who received the investigational product under double blind condition, 280 subjects completed the study (140 subjects in Low dose group and 140 subjects in High dose group), and 8 subjects prematurely terminated the study (3 subjects in Low dose group and 5 subjects in High dose group).

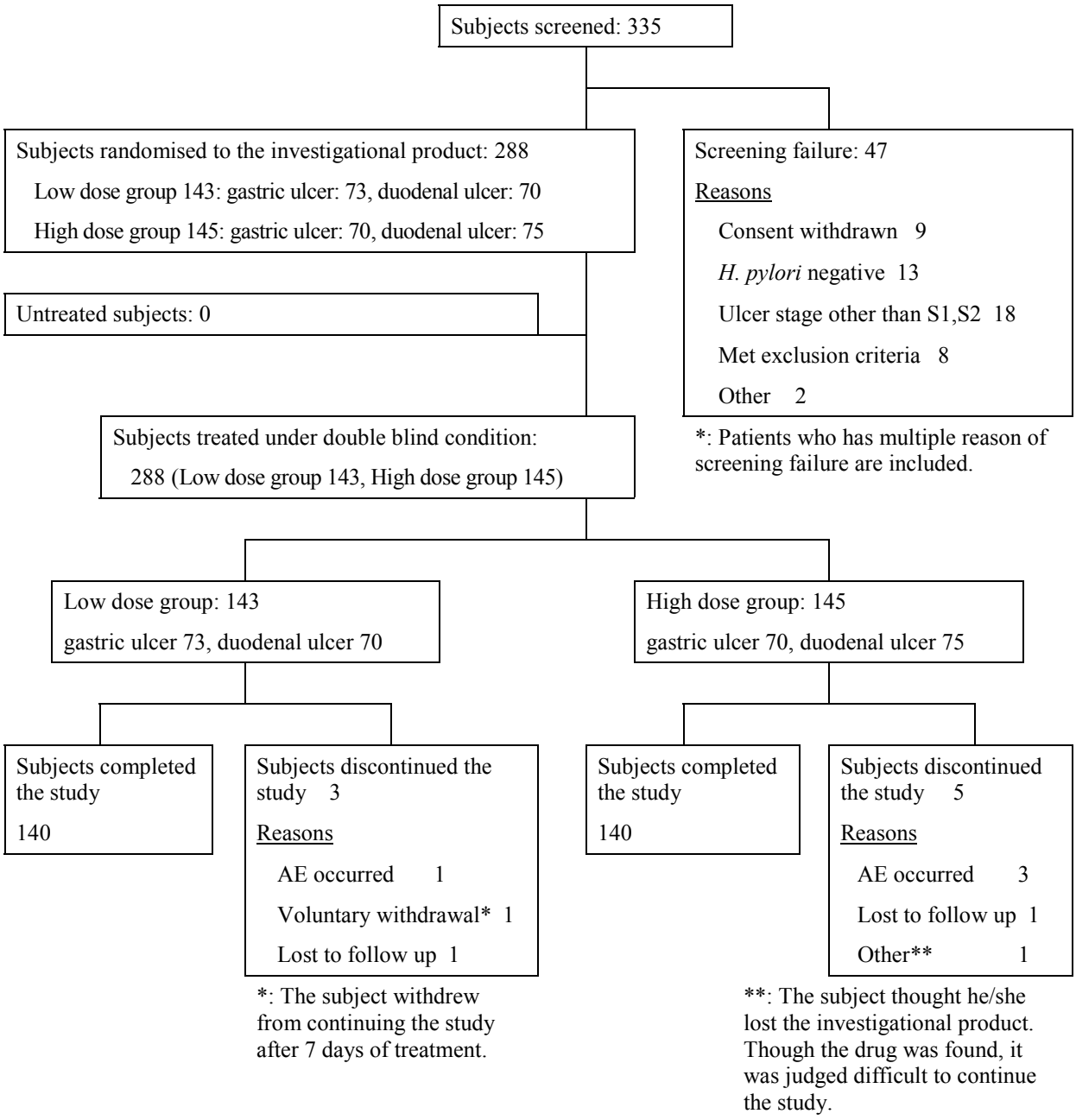

Figure S 1 Disposition of subjects (completed or discontinued subjects)

Efficacy results

Table S 1 shows *H. pylori* eradication rates in Full Analysis Set (FAS). The rates were 81.1% in Low dose group (90% CI: 74.9-86.3%) and 80.0% in High dose group (90% CI: 73.7-85.3%). Since the lower limits of confidence interval for both Low and High dose groups were above the efficacy standard of the guideline[9)] (70%), both groups were confirmed to be an effective therapy for *H. pylori* eradication.

Table S 1 ***H. pylori*** **eradication rate**

	Negative	Positive	Indeterminable	Total	Eradication rate	90%CI
Low dose group	116	24	3	143	81.1%	74.9-86.3%
High dose group	116	24	5	145	80.0%	73.7-85.3%

Table S 2 shows *H. pylori* eradication rates by gastric ulcer and duodenal ulcer. The rates were 86.3% in Low dose group (90% CI: 77.9-92.4%) and 77.1% in High dose group (90% CI: 67.4-85.1%) in patients with gastric ulcer, and 75.7% in Low dose group (90%CI: 65.8-83.9%) and 82.7% in High dose group (90%CI: 73.9-89.4%) in patients with duodenal ulcer.

Table S 2 **H. pylori eradication rate by gastric ulcer and duodenal ulcer**

	Dose group	Negative	Positive	Indeter-minable	Total	Eradication rate	90%CI
Gastric ulcer	Low	63	10	0	73	86.3%	77.9-92.4%
	High	54	12	4	70	77.1%	67.4-85.1%
Duodenal ulcer	Low	53	14	3	70	75.7%	65.8-83.9%
	High	62	12	1	75	82.7%	73.9-89.4%

H. pylori eradication rates by susceptibility to the antimicrobials are shown in Table S 3 (AMPC) and Table S 4 (CAM).

The eradication rates in subjects susceptible to AMPC at pre-treatment were 85.0% in Low dose group and 84.6% in High dose group, the rates in subjects non-susceptible to AMPC at pre-treatment were 65.5% in Low dose group and 60.7% in High dose group.

The eradication rates in subjects susceptible to CAM at pre-treatment were 86.1% in Low dose group and 88.5% in High dose group, the rates in subjects resistant to CAM at pre-treatment were 50.0% in Low dose group and 34.8% in High dose group. There were no subjects presented intermediate susceptibility to CAM before the eradication therapy.

Table S 3 ***H. pylori*** **eradication rate by susceptibility to AMPC**

Dose group	**Susceptibility**	**Negative**	**Positive**	**Indeterminable**	**Total**	**Eradication rate**
Low dose	Susceptible	96	14	3	113	85.0%
	Non-susceptible	19	10	0	29	65.5%
	Unknown	1	0	0	1	100.0%
High dose	Susceptible	99	17	1	117	84.6%
	Non-susceptible	17	7	4	28	60.7%

MIC breakpoint for AMPC was defined as follows: Susceptible: ≤0.03 μg/mL, Non-susceptible: >0.03 μg/mL

Table S 4 *H. pylori* eradication rate by susceptibility to CAM

Dose group	Susceptibility	Negative	Positive	Indeterminable	Total	Eradication rate
Low dose	Susceptible	105	14	3	122	86.1%
	Intermediate	0	0	0	0	
	Resistant	10	10	0	20	50.0%
	Unknown	1	0	0	1	100.0%
High dose	Susceptible	108	12	2	122	88.5%
	Intermediate	0	0	0	0	
	Resistant	8	12	3	23	34.8%

MIC breakpoint for CAM was defined as follows: Susceptible: ≤0.25 μg/mL, Intermediate: 0.5 μg/mL, Non-susceptible: ≥1 μg/mL

Safety results

During the eradication therapy period, adverse events were reported in 67 out of 143 subjects in Low dose group (46.9%, 90% CI: 39.7-54.1%) and 76 of 145 subjects in High dose group (52.4%, 90% CI: 45.3%-59.5%). Adverse events during the observation period were reported in 35 of 142 subjects (24.6%, 90%CI: 18.8%-31.3%) and 40 of 143 subjects (28.0%, 90%CI: 21.8%-34.8%). While slightly lower in Low dose group, the incidences of adverse events were about similar.

No death case was reported in this study. There were 4 serious adverse events reported (1 in Low dose group and 3 in High dose group during the observation period). Since all of them were observed 14 days or more after the last dose of study drug had been given, causual relationship with the investigational product was ruled out.

Table S 5 shows adverse events observed at an incidence of 5% or higher during the eradication therapy period. Adverse events of 5% or higher incidence included diarrhoea (11.9%) and loose stool (11.2%) in Low dose group, and loose stool (21.4%), diarrhoea (12.4%) and dysgeusia (12.4%) in High dose group. Adverse drug reactions of 5% or higher incidence during the eradication therapy period were diarrhoea (11.9%) and loose stool (11.2%) in Low dose group, and loose stool (21.4%), diarrhoea (12.4%) and dysgeusia (12.4%) in High dose group.

Table S 5 Adverse events occurred at an incidence of 5% or higher (eradication therapy period)

Adverse events	Number of subjects (%)					
	Low dose group (n=143)		High dose group (n=145)		Total (n=288)	
Loose stool	16	(11.2)	31	(21.4)	47	(16.3)
Diarrhoea	17	(11.9)	18	(12.4)	35	(12.2)
Dysgeusia	3	(2.1)	18	(12.4)	21	(7.3)

Adverse events observed during the treatment (including abnormal laboratory changes at the end of the treatment) were counted. Those occurred at an incidence of 5% or higher in either group are presented.

Table S 6 shows adverse events observed at an incidence of 5% or higher during the observation period. Adverse events of 5% of higher incidence included only nasopharyngitis (7.7%) in High dose group and there were no adverse events occurred at 5% or higher incidence in Low dose group. No adverse drug reaction of 5% or higher incidence was reported in both Low dose and High dose groups during the observation period.

Table S 6 Adverse events occurred at an incidence of 5% or higher (observation period)

Adverse event	Number of subjects (%)					
	Low dose group (n=142)		High dose group (n=143)		Total (n=285)	
Nasopharyngitis	7	(4.9)	11	(7.7)	18	(6.3)

Observation period: Only adverse events occurred during the observation period were counted.
Those occurred at an incidence of 5% or higher in either group are presented.

Date of the report
9 December 2004