AstraZeneca

Clinical Study Report Synopsis

Drug Substance	D961H
Study Code	D961PC00001
Edition Number	2
Date	5 March 2012

A Phase III Multinational, Multicenter, Randomized, Double-blind, Parallel-group, Comparative Efficacy and Safety Study of D961H (20 mg once daily) Versus Placebo for Prevention of Gastric and/or Duodenal Ulcers Associated with Continuous Low-dose Aspirin (LDA) Use

Final CSR

Study dates: First subject enrolled: 4 February 2010
Last subject completed: 9 November 2011

Phase of development: Therapeutic confirmatory (III)

Study centre(s)

This study was conducted at 57 centres in Japan, Korea and Taiwan.

Publications

None at the time of writing this report.

Objectives and criteria for evaluation

Table S 1 Primary and secondary objectives and outcome variables

Objectives	Outcome variables
Primary: to assess the efficacy of D961H (esomeprazole) 20 mg once daily (q.d.) (hereinafter referred to as D20) versus placebo in continuous treatment involving patients with a history of gastric and/or duodenal ulcers receiving daily low-dose aspirin (LDA) therapy by evaluating time from randomisation to occurrence of gastric and/or duodenal ulcers.	**Primary:** time from randomisation to date of documentation of gastric and/or duodenal ulcers
Secondary: to assess the efficacy of D20 versus placebo in patients with a history of gastric and/or duodenal ulcer receiving daily LDA therapy by evaluating the following:	**Secondary:**
• Presence/absence of gastric and/or duodenal ulcers up to 12, 24, 36, 48, 60 and 72 weeks after randomisation	Presence/absence of gastric and/or duodenal ulcers for up to 12, 24, 36, 48, 60 and 72 weeks after randomisation
• Degree of gastric mucosal lesion evaluated by modified LANZA score at Weeks 12, 24, 36, 48, 60 and 72 after randomisation	Degree of gastric mucosal lesion by modified LANZA score at Weeks 12, 24, 36, 48, 60 and 72 after randomisation
• Presence/absence and severity of reflux esophagitis (RE) evaluated by the Los Angeles (LA) classification at Weeks 12, 24, 36, 48, 60 and 72 after randomisation	Presence/absence and severity of RE evaluated by the LA classification at Weeks 12, 24, 36, 48, 60 and 72 after randomisation
• Presence /absence and severity of gastrointestinal symptoms assessed by investigator(s) at each visit	Presence/absence and severity of gastrointestinal symptoms assessed by the investigator(s) at each visit
Exploratory: to investigate the effect of CYP2C19 polymorphism on the efficacy of D20 in patients with a history of gastric and/or duodenal ulcer receiving daily LDA therapy by evaluating the primary and secondary efficacy outcome variables separately for CYP2C19 genotypes.	**Exploratory:** primary and secondary efficacy outcome variables separately for CYP2C19 genotypes
Safety: to assess safety and tolerability of D20 versus placebo in patients with a history of gastric and/or duodenal ulcers on continuous LDA therapy by evaluating adverse events, clinical laboratory data, and vital signs (blood pressure and pulse rate).	**Safety:** adverse events, clinical laboratory data, and vital signs (blood pressure and pulse rate)
Long term safety: to assess long-term safety and tolerability of D20 during long-term treatment (52 weeks or longer) in patients (100 or more) with a history of gastric and/or duodenal ulcers on continuous LDA therapy by evaluating adverse events, clinical laboratory data, and vital signs (blood pressure and pulse rate).	**Long term safety:** adverse events, clinical laboratory data, and vital signs (blood pressure and pulse rate)

Study design

The study was a multicentre, randomised, double-blind, parallel-group (2 groups), placebo controlled phase III study involving patients with a history of gastric and/or duodenal ulcers receiving daily LDA therapy.

Target subject population and sample size

Target subject population was patients aged 20 years and above with a history of gastric and/or duodenal ulcers who were receiving daily LDA therapy for prevention of thrombosis/embolism. Target sample size was 426.

In order to detect a difference in time to occurrence of peptic ulcer between D20 and placebo with two-sided 2.94% significance level and >90% power, assuming a recruitment period of 12 months and a minimum follow-up of 6 months; ie, the total length of study was estimated to be 18 months, at least 36 events were required. To get the number of events during the period, in total 426 subjects (213 subjects per group) were to be randomised in the study taking 15% of subjects who could discontinue the study without an event into consideration.

A single interim analysis to assess the superiority of D20 to placebo in the time to occurrence of peptic ulcer from randomisation was planned when 18 events had occurred and at least 250 subjects were randomised.

The final analysis of the primary variable was to be performed when 36 events were observed.

Data collection for the long term safety objective was continued until 100 or more subjects in D20 group completed long-term treatment (52 weeks or longer) as required according to the International Conference on Harmonisation (ICH) E1 guideline.

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

In this study the following test product/placebo were used:

- D961H 20 mg capsule (batch number: H1189-04-01-14, 09-004156AZ)
- Placebo for D961H capsule (batch number: H0459-06-03-15, 09-004155AZ)

One capsule of D961H 20 mg or placebo was orally given once daily after breakfast.

Additional study drug

In this study the following additional study drug was used;

- Gefanil Capsule 50®

From randomised day to the last day of speculated visit or day of discontinuation, a capsule of gefarnate 50 mg was taken orally twice a day (after breakfast and after dinner).

Duration of treatment of investigational product, comparator and additional study drug

Up to 72 weeks

Statistical methods

The full analysis set (FAS) and the per-protocol set (PPS) were used to analyse the time to occurrence of gastric and/or duodenal ulcer. Kaplan-Meier plots showing the occurrence-free rate of peptic ulcer against the time from randomisation were prepared. The primary variable (time to occurrence of peptic ulcer) was compared between D20 and placebo using a log-rank test. An interim analysis was to be done at the time at least 18 subjects had an occurrence of peptic ulcer. The multiplicity of the tests due to the interim analysis was adjusted using the Lan-DeMets α-spending function in Pocock plan. Secondarily, the occurrence-free rates of peptic ulcer at the time points of esophagogastroduodenoscopies (EGDs) were also obtained based on the corresponding results of EGD. The FAS was only used to analyse the LANZA scores and the LA classification of RE. Shift tables showing the changes in LANZA scores from pre-dose to post-dose were made. The LANZA scores and the changes from pre-dose at each time-point were summarised for each treatment group using descriptive statistics. The number and the proportion of subjects for each LA classification of RE at Weeks 12, 24, 36, 48, 60 and 72 were summarised for each treatment group. The FAS was also used to analyse the gastrointestinal symptoms. Shift tables presenting the changes from pre-dose to post-dose were prepared. To investigate an effect of CYP2C19 polymorphism on the efficacy of D20, subgroup analyses based on the CYP2C19 genotype were performed for some efficacy outcome variables.

The safety analysis set was used to analyse all safety variables. Safety variables were presented using descriptive statistics.

Subject population

After achieving the criteria to conduct an interim analysis, it was decided to conduct the interim analysis using the data obtained on 26 Feb 2011 (defined as data-cut-off date) or before. In total 798 subjects had been enrolled and 366 subjects had been randomised at the time of date cut-off for the interim analysis. The numbers of subjects with a recurrence of gastric and/or duodenal ulcers were 24 in the FAS and 22 in the FAS by Central Evaluation Committee (CEC). Based on the results of the interim analysis performed on 11 May 2011, the IDMC (Independent Data Monitoring Committee) made a recommendation that the sponsor should stop the comparative analysis. On 19 May 2011, AstraZeneca adopted the recommendation and decided discontinuing the comparative analysis of the study. The results of the interim analysis were reported in the edition 1 of the clinical study report (CSR) dated 2 September 2011.

After the key code break performed on 20 May 2011, the last visit was scheduled for all subjects in the placebo group to complete the study.

Data collection for the long term safety objective was continued until 100 or more subjects in D20 group completed long-term treatment (52 weeks or longer) according to the protocol.

The disposition of subjects and statistical analysis sets are shown in Table S 2 and Table S 3. The descriptive statistics of demographic and other baseline characteristics are shown in Table S 4. Subject recruitment continued by 20 April 2011. Finally, total of 915 subjects were enrolled and 430 subjects were randomised. The demographic and baseline characteristics were well balanced between the two treatment groups. The demographic and baseline characteristics of the FAS by CEC and PPS were similar to those of the FAS.

Table S 2 Disposition of subjects

	D20	Placebo	Total
Subjects enrolled	-	-	914**
Re-enrolled*	-	-	26
Subjects who were not randomised	-	-	484**
Eligibility criteria not fulfilled	-	-	462
Voluntary discontinuation by subject	-	-	21**
Other	-	-	1
Subjects who were randomised	215	215	430
Re-enrolled*	11	9	20
Subjects who completed the study	164	137	301
Subjects who discontinued study	51	78	129
Adverse event	17	22	39
Voluntary discontinuation by subject	17	12	29
Lost to follow-up	1	1	2
Severe non-compliance to protocol	0	1	1
Condition under investigation worsened	0	1	1
Development of study-specific withdrawal criteria	7	33	40
Other	9	8	17

Data derived from Section 11.1, Table 11.1.1

* See the exclusion criterion No.11 in Section 5.3.2 in the CSR for details.

** It was found after the database lock that 1 subject who was not randomised due to voluntary discontinuation (E2003019) was not entered in the study database accidentally. The study database was not revised since this was considered as a non-critical error (Table S 2 does not include the subject).

Table S 3 Statistical analysis sets

	D20	Placebo	Total
Randomised	215	215	430
Subjects included in Safety analysis set*	213 (99.1%)*	214 (99.5%)*	427 (99.3%)
Subjects included in FAS	213 (99.1%)	214 (99.5%)	427 (99.3%)
Subjects included in FAS by CEC	200 (93.0%)	206 (95.8%)	406 (94.4%)
Subjects included in PPS	146 (67.9%)	145 (67.4%)	291 (67.7%)

FAS: Full analysis Set, CEC: Central evaluation committee, PPS: Per-protocol set
Data derived from Section 11.1, Table 11.1.3

* One subject who was randomised to placebo group was prescribed D20 by mistake. Since this subject considered as a subject in D20 group in the safety analysis, the numbers of subjects in each treatment group were 214 (D20 group) and 213 (placebo group) in the safety analysis in this CSR.

Table S 4 Descriptive statistics of demographic and other baseline characteristics (FAS)

Variable	Category/status	D20 (n=213)	Placebo (n=214)	Total (n=427)
Sex	Male	170 (79.8%)	168 (78.5%)	338 (79.2%)
	Female	43 (20.2%)	46 (21.5%)	89 (20.8%)
Age (years)	≤64	85 (39.9%)	71 (33.2%)	156 (36.5%)
	≥65 to ≤74	82 (38.5%)	89 (41.6%)	171 (40.0%)
	≥75	46 (21.6%)	54 (25.2%)	100 (23.4%)
Age (years)	Mean (SD)	66.4 (9.9)	68.2 (9.0)	67.3 (9.5)
	Median	68.0	69.0	69.0
	Min – Max	38 - 85	36 - 88	36 - 88
Ethnic group	Asian (other than Chinese and Japanese)	33 (15.5%)	33 (15.4%)	66 (15.5%)
	Chinese	21 (9.9%)	21 (9.8%)	42 (9.8%)
	Japanese	159 (74.6%)	160 (74.8%)	319 (74.7%)
H. pylori status	Negative	117 (54.9%)	116 (54.2%)	233 (54.6%)
	Positive	93 (43.7%)	93 (43.5%)	186 (43.6%)
	Missing	3 (1.4%)	5 (2.3%)	8 (1.9%)
Genotype of CYP2C19	Homo extensive metaboliser	71 (33.3%)	79 (36.9%)	150 (35.1%)
	Hetero extensive metaboliser	113 (53.1%)	90 (42.1%)	203 (47.5%)
	Poor metaboliser	26 (12.2%)	40 (18.7%)	66 (15.5%)
History of gastric ulcer	Yes	132 (62.0%)	139 (65.0%)	271 (63.5%)
	No	81 (38.0%)	75 (35.0%)	156 (36.5%)
History of duodenal ulcer	Yes	90 (42.3%)	87 (40.7%)	177 (41.5%)
	No	123 (57.7%)	127 (59.3%)	250 (58.5%)
LDA dosage	81 mg	29 (13.6%)	26 (12.1%)	55 (12.9%)
	100 mg	173 (81.2%)	179 (83.6%)	352 (82.4%)
	>100 mg	11 (5.2%)	9 (4.2%)	20 (4.7%)
Duration of LDA intake prior to this study	<2 weeks	15 (7.0%)	24 (11.2%)	39 (9.1%)
	2-4 weeks	3 (1.4%)	5 (2.3%)	8 (1.9%)
	>4 weeks	195 (91.5%)	185 (86.4%)	380 (89.0%)
Reason for LDA treatment	Primary prevention of cardiovascular and cerebrovascular disease	69 (32.4%)	70 (32.7%)	139 (32.6%)
	Secondary prevention of cardiovascular and cerebrovascular disease	141 (66.2%)	142 (66.4%)	283 (66.3%)
	Other	3 (1.4%)	2 (0.9%)	5 (1.2%)

LDA: Low-dose aspirin, SD: Standard deviation
Data derived from Section 11.1, Table 11.1.4.1

Summary of efficacy results

In total, 2 subjects in D20 group and 22 subjects in placebo group experienced a recurrence of peptic ulcers up to Week 48 at the date of data-cut off for the interim analysis. There was a statistically significant difference in the time from randomisation to occurrence of gastric or duodenal ulcer between D20 group and placebo group in the FAS ($p<0.001$, Log-rank test). The similar results were obtained in other analysis sets, ie, FAS by CEC and PPS. The results of the secondary variables supported those of the primary variable well (see CSR for the interim analysis).

On 20 May 2011, all subjects were unblinded their treatment. Finally, 4 subjects in D20 group and 27 subjects in placebo group experienced a recurrence of peptic ulcer until the key code break. EGD data were collected up to Week 60 by the date of the key code break.

Gastric and/or duodenal ulcer-free estimated rates by the Kaplan-Meier method (FAS) are summarised in Table S 5. The Kaplan-Meier curves showing the gastric and/or duodenal ulcer-free rates against time are illustrated in Figure S 1.

The estimated ulcer-free rate in the D20 group was sustained high through 60 weeks without marked change.

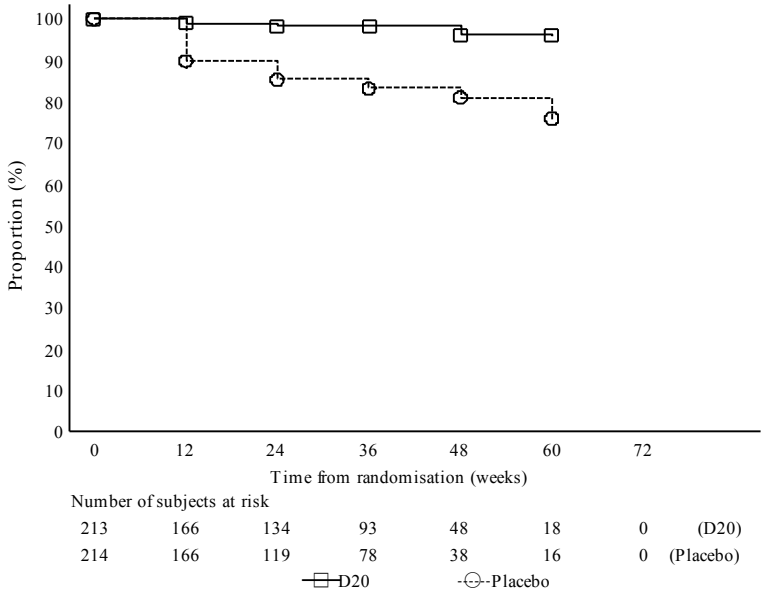
The similar results were obtained in the analysis based on the final data including the recurrence of peptic ulcer after the key code break. A total of 8 subjects (2 in the D20 and 6 in the placebo group) experienced a recurrence of peptic ulcer after the key code break (the 6 events in the placebo group were confirmed by EGD performed at the last visit). Finally, the numbers of subjects who had a recurrence of peptic ulcers during the study were 6 and 33 subjects in the D20 and placebo group, respectively.

Table S 5 Gastric and/or duodenal ulcer-free rate by Kaplan-Meier method (FAS) (key open data)

Time	Estimated rate (96.65% CI)		Hazard ratio (96.65% CI) (vs placebo)	Log-rank test (vs placebo)
	D20 (n=213)	Placebo (n=214)		
Week 12	98.8 (97.0, 100.0)	89.8 (84.8, 94.8)		
Week 24	98.1 (95.7, 100.0)	85.2 (79.1, 91.3)		
Week 36	98.1 (95.7, 100.0)	83.0 (76.3, 89.8)	0.14 (0.04, 0.42)	p<0.001
Week 48	96.0 (91.1, 100.0)	80.9 (72.8, 88.9)		
Week 60	96.0 (91.1, 100.0)	75.8 (63.0, 88.7)		

CI: Confidence interval
Data derived from Section 11.2, Table 11.2.1.2.1.1 and Table 11.2.2.1.1.1

Figure S 1 Gastric and /or duodenal ulcer-free rate by Kaplan-Meier method (FAS)



Data derived from Section 11.2, Figure 11.2.1.1.1.1

Summary of safety results

The mean duration of treatment in the D20 and placebo group were 293.0 days and 208.9 days, respectively. The extent of exposure was 40.3% higher in the D20 group then that in the placebo group. This is due to the higher rate of discontinuation for occurrence of ulcer and due to the scheduled completion of the placebo group after the date of the key code break.

The frequency of reported adverse events (AEs) were 72.4% in the D20 group and 65.3% in the placebo group (Table S 6). The most commonly reported AEs were shown in Table S 7. In general, the differences in reporting frequency between the two treatment groups were small and not assessed as clinically relevant.

Table S 6 Number of subjects who had at least 1 AE in any category, and total numbers of AEs (safety analysis set)

Category of AE	Number of subjects who had an AE [a]			
	D20 (n=214)		Placebo (n=213)	
Mean number of Treatment days	**293.0**		**208.9**	
Adverse event	155	(72.4%)	139	(65.3%)
Serious adverse event leading to death	0		0	
Serious adverse event not leading to death	17	(7.9%)	15	(7.0%)
Adverse event leading to discontinuation of study treatment	17	(7.9%)	22	(10.3%)
Other significant adverse event [b]	0		0	
Drug-related adverse event [c]	31	(14.5%)	29	(13.6%)
Severe adverse event	7	(3.3%)	10	(4.7%)
	Total number of AEs [d]			
Adverse event	479		429	
Serious adverse event leading to death	0		0	
Serious adverse event not leading to death	19		17	
Adverse event leading to discontinuation of study treatment	17		26	
Other significant adverse event [b]	0		0	
Drug-related adverse event [c]	37		43	
Severe adverse event	8		11	

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: Significant AEs, other than SAEs and those AEs leading to discontinuation of study treatment, which are of particular clinical importance, are identified an and classified as Other Significant AEs (OAEs).
c: Related AEs are those for which there was a possible relationship to investigational product as judged by the investigator.
d: Multiple occurrences of AEs on a particular preferred term level in the same subject is counted as 1 occurrence.
Data derived from Section 11.3, Table 11.3.1.1, Table 11.3.2.1.1 and Table 11.3.2.1.11

Table S 7 Number (%) of subjects with the most commonly reported adverse events in any treatment group (Safety analysis set)

System organ class Preferred term	D20 (n=214)	Placebo (n=213)
Subjects with any AE	155 (72.4)	139 (65.3)
GASTROINTESTINAL DISORDERS	**78 (36.4)**	**74 (34.7)**
CONSTIPATION	12 (5.6)	11 (5.2)
GASTRIC POLYPS	11 (5.1)	1 (0.5)
DIARRHOEA	10 (4.7)	7 (3.3)
ABDOMINAL PAIN UPPER	5 (2.3)	7 (3.3)
GASTRITIS EROSIVE	5 (2.3)	9 (4.2)
DUODENITIS	4 (1.9)	11 (5.2)
GASTRITIS	4 (1.9)	7 (3.3)
ABDOMINAL DISTENSION	4 (1.9)	6 (2.8)
DENTAL CARIES	4 (1.9)	6 (2.8)
EROSIVE DUODENITIS	0 (0.0)	7 (3.3)
INFECTIONS AND INFESTATIONS	**59 (27.6)**	**53 (24.9)**
NASOPHARYNGITIS	43 (20.1)	30 (14.1)
UPPER RESPIRATORY TRACT INFECTION	6 (2.8)	4 (1.9)
PHARYNGITIS	2 (0.9)	5 (2.3)
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	**35 (16.4)**	**16 (7.5)**
BACK PAIN	8 (3.7)	3 (1.4)
MUSCULOSKELETAL PAIN	6 (2.8)	0 (0.0)
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	**21 (9.8)**	**17 (8.0)**
UPPER RESPIRATORY TRACT INFLAMMATION	6 (2.8)	2 (0.9)
RHINITIS ALLERGIC	4 (1.9)	5 (2.3)
COUGH	2 (0.9)	5 (2.3)
NERVOUS SYSTEM DISORDERS	**20 (9.3)**	**11 (5.2)**
HEADACHE	5 (2.3)	4 (1.9)
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	**18 (8.4)**	**18 (8.5)**
ECZEMA	4 (1.9)	7 (3.3)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	**16 (7.5)**	**11 (5.2)**
OEDEMA PERIPHERAL	7 (3.3)	5 (2.3)
METABOLISM AND NUTRITION DISORDERS	**15 (7.0)**	**12 (5.6)**
DIABETES MELLITUS	5 (2.3)	5 (2.3)
HEPATOBILIARY DISORDERS	**9 (4.2)**	**3 (1.4)**
HEPATIC FUNCTION ABNORMAL	5 (2.3)	0 (0.0)
VASCULAR DISORDERS	**8 (3.7)**	**10 (4.7)**
HYPERTENSION	5 (2.3)	7 (3.3)

Table S 7 Number (%) of subjects with the most commonly reported adverse events in any treatment group (Safety analysis set)

System organ class Preferred term	D20 (n=214)	Placebo (n=213)
EAR AND LABYRINTH DISORDERS	**5 (2.3)**	**8 (3.8)**
VERTIGO	1 (0.5)	5 (2.3)

A cut off of 2% has been used.
System organ class (SOC), Preferred term (PT): MedDRA version 13.1
Number (%) of subjects with AEs, sorted by SOC followed by PT in decreasing order of frequency (sorted by total number on D20).
Data derived from Section 11.3, Table 11.3.2.2.1

A total of 32 subjects reported one or more SAEs not leading to death; 17 (7.9%) subjects in D20 group and 15 (7.0%) subjects in placebo group. There were no SAEs in the D20 group where the investigator considered that there was a possible relationship to investigational product. Eleven (11) subjects discontinued study treatment permanently due to an SAE, 6 in the D20 group and 5 in the placebo group.

Thirty-nine (39) subjects discontinued study treatment due to an AE, 17 (7.9%) in D20 group and 22 (10.3%) in placebo group.

There were no clinically meaningful differences between the two treatment groups with regard to laboratory values or vital signs.