AstraZeneca

Clinical Study Report Synopsis

Drug Substance	D961H
Study Code	D961HC00001
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A Phase III, Multicentre, Randomised, Double-blind, Parallel-group, Comparative Efficacy and Safety Study of D961H (20 mg once daily) Versus Placebo for the Prevention of Gastric and/or Duodenal Ulcers Associated with Daily Nonsteroidal Anti-inflammatory Drug (NSAIDs) Use

Study dates: First subject enrolled: 27 August 2007
Last subject completed: 17 February 2009

Phase of development: Therapeutic confirmatory (III)

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

Study centre(s)

This study was conducted at 57 centres in Japan.

Publications

None at the time of writing this report.

Objectives

The primary objective of this study was to assess the efficacy of D961H 20 mg once daily (D20) versus placebo for up to 24 weeks of treatment involving patients with a history of gastric and/or duodenal ulcers receiving daily nonsteroidal anti-inflammatory drug (NSAID) therapy by evaluating presence or absence of gastric and/or duodenal ulcer throughout the treatment period in terms of efficacy on prevention of gastric and/or duodenal ulcers.

The secondary objectives of this study were as follows:

- To assess the efficacy of D20 versus placebo in patients with a history of gastric and/or duodenal ulcer receiving daily NSAID therapy by evaluating the followings:
  - Presence/absence of gastric and/or duodenal ulcers for up to 4 weeks and 12 weeks after randomisation
  - Severity of gastric mucosal lesion evaluated by modified LANZA score (Lanza FL, et al., 1988) at Weeks 4, 12, and 24 after randomisation
  - Presence/absence and severity of NSAID-associated gastrointestinal (GI) symptoms assessed by investigator(s) at Weeks 4, 8, 12, 16, 20, and 24 after randomisation
- To assess the safety of D20 versus placebo after the long-term (24 weeks) treatment in patients with a history of gastric and/or duodenal ulcers receiving daily NSAID therapy by evaluating AEs, clinical laboratory values, and vital signs.

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 NSAID therapy.

Target subject population and sample size

Male or female patients aged 20 years or over with a history of gastric and/or duodenal ulcers with ulcer scar confirmed by the esophagogastroduodenoscopy (EGD) performed at screening who were receiving daily NSAID therapy.

A total of 340 subjects were to be randomised in the study (170 subjects each in the D20 and placebo group, respectively).

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

In this study the following test products were used:

- D961H 20 mg-capsules

  One capsule of D961H capsule 20 mg was orally administered once daily after breakfast for 24 weeks in subjects randomised into the D20 group.

Comparator, dosage and mode of administration

In this study the following comparator were used:

- Placebo for D961H capsule (placebo comes in unidentifiable capsules with D961H 20 mg capsules)

  One capsule of placebo capsule was orally administered once daily after breakfast for 24 weeks in subjects randomised into the placebo group.

Duration of treatment

24 weeks

Criteria for evaluation - efficacy and pharmacokinetics (main variables)

- **Primary outcome variable:**
  - Presence or absence of gastric and/or duodenal ulcers throughout the treatment period
- **Secondary outcome variables:**
  - Presence or absence of gastric and/or duodenal ulcers for up to 4 weeks and 12 weeks after randomisation
  - Severity of gastric mucosal lesion by modified LANZA score at Weeks 4, 12, and 24 after randomisation
  - Presence/absence and severity of NSAID-associated gastrointestinal (GI) symptoms assessed by investigator(s) at Weeks 4, 8, 12, 16, 20, and 24 after randomisation

Criteria for evaluation - safety (main variables)

- AEs
- Clinical laboratory values

- Vital signs

Statistical methods

The estimated ulcer-free rate by Kaplan-Meier method was considered to be the primary efficacy analysis for this study.

The Kaplan-Meier method was used to estimate the time-to-event curves for maintenance of ulcer free status. In this estimation, days from the randomisation were grouped into the following intervals: Day 0, Days 1-32, Days 33-60, Days 61-91, Days 92-119, Days 120-147, Days 148-175. Even if a subject had an event after Day 175, then the subject's data was treated as censored on Day 175. From the time-to-event-curves, the ulcer-free rate at Week 24 (ie, Day 175) was obtained for each treatment group together with its 95% Confidence interval (CI) using the Greenwood formula. The time-to-event curves for maintenance of ulcer-free status were compared between D20 and placebo using a log-rank test.

The ulcer-free observed rate at Week 24 was obtained for each treatment group together with the two-sided 95% CI using the Newcombe-Wilson score method without continuity correction (Newcombe R, 1998). The ulcer-free rates at Week 24 were compared between D20 and placebo using a chi-square test without continuity correction.

For safety variables, quantitative data were summarised for each treatment group using descriptive statistics and qualitative data were summarised for each treatment group using a frequency table.

Subject population

The demographic characteristics of the study population in the FAS (Full analysis set) are described in Table S 1. The demographic and baseline characteristics were well balanced between the two treatment groups. The demographic and baseline characteristics of the FAS by CEC (Central Evaluation Committee) and PPS (Per-protocol set) were similar to those of the FAS.

Table S 1 Subject population and disposition (FAS)

		D20 (n=173)	Placebo (n=168)	Total (n=341)
Subjects enrolled		-	-	1246
Re-enrolled		-	-	69
Subjects who were not randomised		-	-	903
Did not meet eligibility criteria		-	-	877
Adverse event		-	-	1
Voluntary Discontinuation by Subject		-	-	24
Other		-	-	1
Number of subjects who were randomised		175	168	343
Number of subjects who completed study		134	90	224
Number of subjects who discontinued study		41	78	119
Number of subjects (%) included in Safety analysis set		173 (98.9%)	168 (100.0%)	341 (99.4%)
Number of subjects (%) included in FAS		173 (98.9%)	168 (100.0%)	341 (99.4%)
Number of subjects (%) included in FAS by CEC		159 (90.9%)	147 (87.5%)	306 (89.2%)
Number of subjects (%) included in PPS		149 (85.1%)	149 (88.7%)	298 (86.9%)
Sex	Male	65 (37.6%)	68 (40.5%)	133 (39.0%)
	Female	108 (62.4%)	100 (59.5%)	208 (61.0%)
Age (years)	≤64	78 (45.1%)	91 (54.2%)	169 (49.6%)
	≥65 to ≤74	59 (34.1%)	54 (32.1%)	113 (33.1%)
	≥75	36 (20.8%)	23 (13.7%)	59 (17.3%)
Age (years)	Mean (SD)	63.6 (12.2)	62.4 (12.3)	63.0 (12.2)
	Median	65.0	64.0	65.0
	Min – Max	33 – 86	24 – 90	24 – 90
Type of arthritic disease	Rheumatoid arthritis	54 (31.2%)	48 (28.6%)	102 (29.9%)
	Osteoarthritis	44 (25.4%)	32 (19.0%)	76 (22.3%)
	Other chronic condition [a]	75 (43.4%)	88 (52.4%)	163 (47.8%)
Chronic condition history (years)	Mean (SD)	6.9 (8.6)	5.9 (7.4)	6.4 (8.0)
	Median	4.0	4.0	4.0
	Min – Max	0 – 54	0 – 50	0 – 54
Helicobacter pylori status	Negative	76 (43.9%)	82 (48.8%)	158 (46.3%)
	Positive	97 (56.1%)	86 (51.2%)	183 (53.7%)
Degree of gastric mucosa atrophy	Positive	39 (22.5%)	33 (19.6%)	72 (21.1%)
	Negative	133 (76.9%)	135 (80.4%)	268 (78.6%)
	Unknown	1 (0.6%)	0 (0.0%)	1 (0.3%)
Genotype of CYP2C19	Poor metaboliser	35 (20.2%)	39 (23.2%)	74 (21.7%)
	Hetero extensive metaboliser	80 (46.2%)	74 (44.0%)	154 (45.2%)
	Homo extensive metaboliser	58 (33.5%)	54 (32.1%)	112 (32.8%)
	Unknown	0 (0.0%)	1 (0.6%)	1 (0.3%)

FAS: Full analysis Set. CEC: Central evaluation committee. PPS: Per-protocol set
[a]: Lumbago and cervical spondylosis are the main reasons for other chronic condition in type of arthritic disease.

The most common reasons for discontinuation of the study were:

- Adverse event; 18 and 17* in the D20 and placebo group.
  *: Short by 4 subjects; The four subjects were calculated in "Other" since they also had recurrence of gastric ulcer.

- Other; 8 and 57 in the D20 and placebo group (most of them were due to recurrence of gastric ulcer; 6 and 56 in the D20 and placebo group).

Summary of efficacy results

The estimated ulcer-free rate at Week 24 was statistically higher in the D20 group compared to the placebo group (96.0% for D20 and 64.4% for placebo, $p<0.001$, Log-rank test). Also, the ulcer-free observed rate at Week 24 was significantly higher in the D20 group compared to placebo group (96.5% for D20 and 66.7% for placebo, $p<0.001$, Chi-square test). The primary result of the study showed D20 maintained a higher ulcer-free rate compared with placebo. The effect of D20 was evident from after 4 weeks of treatment and remained statistically significant throughout 24 weeks treatment period. In addition, this was also proven in other analysis sets, ie, FAS by central evaluation committee and PPS. The results of the secondary variable, presence or absence of gastric and/or duodenal ulcers and severity of gastric mucosal lesion by modified LANZA score supported the results of the primary variable.

Table S 2 Summary of efficacy results

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

Time	Statistic	D20 (n=173)	Placebo (n=168)
Week 4	Estimated rate [95% CI]	99.4 [98.2, 100.0]	78.8 [72.6, 85.0]
Week 12	Estimated rate [95% CI]	96.7 [93.8, 99.5]	69.4 [62.3, 76.6]
Week 24	Estimated rate [95% CI]	96.0 [92.8, 99.1]	64.4 [56.8, 71.9]
-	Log-rank test (vs placebo)	p<0.001	-

Gastric and/or duodenal ulcer-free observed rate (FAS)

Time	Statistic	D20 (n=173)	Placebo (n=168)
Week 4	Observed rate [95% CI]	99.4 (172/173) [96.8, 99.9]	79.2 (133/168) [72.4, 84.6]
	Chi-square test (vs placebo)	p<0.001	-
Week 12	Observed rate [95% CI]	97.1 (168/173) [93.4, 98.8]	70.8 (119/168) [63.6, 77.2]
	Chi-square test (vs placebo)	p<0.001	-
Week 24	Observed rate [95% CI]	96.5 (167/173) [92.6, 98.4]	66.7 (112/168) [59.2, 73.4]
	Chi-square test (vs placebo)	p<0.001	-

Occurrence of gastric and/or duodenal ulcer (FAS)

Time	Ulcer type	D20 (n=173)	Placebo (n=168)
Week 4	Gastric only	0.6 (1/173)	16.7 (28/168)
	Duodenal only	0.0 (0/173)	2.4 (4/168)
	Gastric & Duodenal	0.0 (0/173)	1.8 (3/168)
Week 12	Gastric only	2.3 (4/173)	23.8 (40/168)
	Duodenal only	0.6 (1/173)	3.6 (6/168)
	Gastric & Duodenal	0.0 (0/173)	1.8 (3/168)
Week 24	Gastric only	2.9 (5/173)	28.0 (47/168)
	Duodenal only	0.6 (1/173)	3.6 (6/168)
	Gastric & Duodenal	0.0 (0/173)	1.8 (3/168)

Shift table of modified LANZA scores at last EGD (FAS) *

Time	Severity	D20					Placebo				
		Baseline					Baseline				
		0	+1	+2	+3	+4	0	+1	+2	+3	+4
Last	0	78	9	26	3	1	41	2	19	0	0
	+1	1	5	6	4	0	8	0	4	0	0
	+2	9	1	10	3	1	12	4	14	3	0
	+3	1	0	1	0	0	0	1	1	3	0
	+4	3	0	1	1	2	29	7	11	6	0

CI: Confidence interval
* Subjects with a measurement at baseline and at least 1 subsequent variable measurement

Summary of safety results

The frequency of reported AEs was similar between the two treatment groups, 77.5% in the D20 group and 73.8% in the placebo group (Table S 3). The most commonly reported AEs were shown in Table S 4. In general, the differences in reporting frequency between the two treatment groups were small and not assessed as clinically relevant.

Table S 3 Number of subjects who had at least 1 adverse event in any category, and total numbers of adverse events (safety analysis set) [a]

Category of adverse event	Number of subjects who had an adverse event a			
	D20 (n=173)		Placebo (n=168)	
Mean number of Treatment days	**142.3**		**116.0**	
Adverse event	134	(77.5)	124	(73.8)
Serious adverse event leading to death	0		0	
Serious adverse event not leading to death	12	(6.9)	5	(3.0)
Adverse event leading to discontinuation of study treatment	18	(10.4)	21	(12.5)
Other significant adverse event [b]	0		0	
Related adverse event [c]	24	(13.9)	27	(16.1)
Severe adverse event	2	(1.2)	3	(1.8)
	Total number of adverse events [d]			
Adverse event	389		345	
Serious adverse event not leading to death	12		7	
Adverse event leading to discontinuation of study treatment	18		29	
Related adverse event [e]	35		34	
Severe adverse event	2		3	

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.
e: Related AEs are those for which there was a possible relationship to investigational product as judged by the investigator.

Table S 4 Number (%) of subjects with the most commonly reported adverse events in any treatment group (Safety analysis set)

Preferred term	D20 (n=173)		Placebo (n=168)	
Nasopharyngitis	27	(15.6)	27	(16.1)
Abdominal pain upper	18	(10.4)	22	(13.1)
Abdominal distension	15	(8.7)	11	(6.5)
Stomach discomfort	15	(8.7)	17	(10.1)
Nausea	11	(6.4)	9	(5.4)
Anorexia	11	(6.4)	6	(3.6)
Reflux oesophagitis	10	(5.8)	13	(7.7)
Diarrhoea	9	(5.2)	6	(3.6)
Constipation	7	(4.0)	5	(3.0)
Dyspepsia	7	(4.0)	10	(6.0)
Back pain	7	(4.0)	3	(1.8)
Rheumatoid arthritis	7	(4.0)	1	(0.6)
Hepatic function abnormal	6	(3.5)	1	(0.6)
Hypertension	6	(3.5)	5	(3.0)
Pharyngitis	3	(1.7)	5	(3.0)

A cut off of 3% has been used.
Preferred term (PT): MedDRA version 11.1
Number (%) of subjects with AEs, sorted by PT in decreasing order of frequency (sorted by total number on D961H).

There were no deaths in the study. A total of 17 subjects reported one or more SAEs not leading to death; 12 subjects in the D20 group and 5 subjects in placebo group. There were 3 SAEs in 3 subjects in the D20 group where the investigator considered that there was a possible relationship to investigational product; pyelonephritis, gastric cancer and lumbar spinal stenosis. The severity of the 3 SAEs was mild or moderate in intensity. Eight subjects discontinued study treatment due to an SAE, 5 in the D20 group and 3 in the placebo group.

The numerical difference in reporting frequency between the two treatment groups were not assessed as clinically significant.

A total of 39 subjects were discontinued study treatment due to AEs; 18 subjects in the D20 group and 21 subjects in the placebo group.

There were no clinically meaningful differences between the two treatment groups with respect to the subjects experiencing changes in laboratory values or vital signs.

Date of the report

15 July 2009