AstraZeneca

Clinical Study Report Synopsis

Drug Substance	D961H
Study Code	D961HC00002
Edition Number	1
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A multicentre, randomised, double-blind, parallel-group, comparative study to compare the efficacy and safety of D961H 20 mg and 40 mg once daily oral administration with omeprazole 20 mg once daily oral administration in patients with reflux esophagitis

Study dates: First subject enrolled: 11 December 2007
Last subject completed: 12 December 2008

Phase of development: Therapeutic confirmatory (III)

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

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Study centre(s)

This study was conducted at 58 centres in Japan.

Publications

None at the time of writing this report.

Objectives

The primary objective of this study was to evaluate the efficacy of D961H 20 mg once daily (D20) and 40 mg once daily (D40) for 8 weeks on healing of RE in patients with reflux esophagitis (RE) in comparison with omeprazole 20 mg once daily (O20) by assessment of presence/absence of RE at Week 8 according to the LA classification.

The secondary objectives of the study were as follows:

- To evaluate the efficacy of D20 and D40 on healing of RE in comparison with O20 by assessment of presence/absence of RE at Week 4 according to the LA classification.
- To evaluate the efficacy of D20 and D40 on GERD symptoms in comparison with O20 by assessment of presence/absence and severity of the patient-reported symptoms.
- To evaluate the effect of D20, D40 and O20 on HRQOL by assessment of HRQOL using “Quality of Life in Reflux and Dyspepsia patients (QOLRAD)”.
- To evaluate the safety and tolerability of D20, D40 and O20 by assessment of adverse events (AEs), laboratory test values and vital signs (blood pressure and pulse rate).

Study design

This was a multicentre, randomised, double-blind, double dummy, parallel-three group study to evaluate the efficacy and safety of D20, D40 and O20 in patients with RE.

Target subject population and sample size

Male and female patients aged 20 years or over with RE endoscopically verified Grade A, B, C or D by LA classification within 1 week prior to initiation of the investigational product administration.

A total of 555 subjects including at least 100 subjects with grade C or D RE according to LA classification were to be enrolled.

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

In this study, the following products were used.

- D961H capsule 20 mg

  One capsule of D961H capsule 20 mg and 2 tablets of omeprazole tablet placebo were orally administered once daily after breakfast for a maximum of 8 weeks in subjects randomised into the D20 group.

- D961H capsule 40 mg
  One capsule of D961H capsule 40 mg and 2 tablets of omeprazole tablet placebo were orally administered once daily after breakfast for a maximum of 8 weeks in subjects randomised into the D40 group.

Comparator, dosage and mode of administration

- Omeprazole tablet 10 mg
  Two tablets of omeprazole tablet 10 mg and 1 capsule of D961H capsule placebo were orally administered once daily after breakfast for a maximum of 8 weeks in subjects randomised into the O20 group.

Duration of treatment

A maximum of 8 weeks

Criteria for evaluation - efficacy and pharmacokinetics (main variables)

– **Primary outcome variable:**

- Presence/absence of RE at Week 8 according to LA classification.

– **Secondary outcome variables:**

[Healing of RE]

- Presence/absence of RE at Week 4 according to LA classification.

[GERD symptoms]

- Time to sustained resolution of each GERD symptom (definition: number of days from the starting day of investigational product administration up to the first day of 7 consecutive days free of that symptom).

- Time to sustained resolution of all GERD symptoms (definition: number of days from the starting day of investigational product administration up to the first day of 7 consecutive days free of all symptoms).

- The proportion of subjects without each GERD symptom during the 7 days preceding visits at Week 1, 2, 4 and 8.

- The proportion of subjects without each GERD symptom or with 'Mild' GERD symptoms up to 1 day during the 7 days preceding visit at Week 1, 2, 4 and 8.

[Patient reported outcomes (PROs)]

- QOLRAD

Criteria for evaluation - safety (main variables)

- AEs

- Laboratory test values

- Vital signs (blood pressure, pulse rate)

Statistical methods

The healing rate of RE at Week 8 and its two-sided 95% confidence interval were calculated for each group. The difference in healing rates between the D40 group and O20 group (D40 group – O20 group) and that between the D20 group and O20 group (D20 group – O20 group) as well as respective two-sided 95% confidence intervals were obtained. It would be concluded that the non-inferiority of D40 to O20 was verified if the lower limit of the two-sided 95% confidence interval of the difference between D40 group and O20 group exceeded -10%. If the non-inferiority of D40 to O20 was verified, verification of the non-inferiority of D20 to O20 would be investigated similarly. The healing rate at Week 8 was compared between D40 group and O20 group and between D20 group and O20 group using Cochran-Mantel-Haenszel test stratified by the baseline LA classification or CYP2C19 genotype. In these comparisons, the significant level was not adjusted.

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 among the three 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)

		D40 (n=190)	D20 (n=189)	O20 (n=190)	Total (n=569)
Number of subjects who were randomised		191	190	191	572
Number of subjects who completed study		179	176	180	535
Number of subjects who discontinued study		12	14	11	37
Number of subjects (%) included in Safety analysis set		190	189	190	569
Number of subjects (%) included in FAS		190	189	190	569
Number of subjects (%) included in FAS by CEC		179	176	183	538
Number of subjects (%) included in PPS		177	176	179	532
Sex	Male	139 (73.2%)	137 (72.5%)	134 (70.5%)	410 (72.1%)
	Female	51 (26.8%)	52 (27.5%)	56 (29.5%)	159 (27.9%)
Age (years)	≤64	127 (66.8%)	135 (71.4%)	126 (66.3%)	388 (68.2%)
	≥65 to ≤74	47 (24.7%)	36 (19.0%)	44 (23.2%)	127 (22.3%)
	≥75	16 (8.4%)	18 (9.5%)	20 (10.5%)	54 (9.5%)
	Mean (Standard deviation)	57.8 (12.8)	57.0 (13.4)	56.5 (14.2)	57.1 (13.5)
	Median	59.0	57.0	57.0	58.0
	Minimum – Maximum	27 – 90	23 – 91	21 – 94	21 – 94
Recurrent reflux esophagitis	No	133 (70.0%)	126 (66.7%)	130 (68.4%)	389 (68.4%)
	Yes	57 (30.0%)	63 (33.3%)	60 (31.6%)	180 (31.6%)
Helicobacter pylori status	Negative	141 (74.2%)	145 (76.7%)	137 (72.1%)	423 (74.3%)
	Positive	49 (25.8%)	44 (23.3%)	53 (27.9%)	146 (25.7%)
Genotype of CYP2C19	Poor metaboliser	29 (15.3%)	32 (16.9%)	26 (13.7%)	87 (15.3%)
	Hetero extensive metaboliser	92 (48.4%)	96 (50.8%)	94 (49.5%)	282 (49.6%)
	Homo extensive metaboliser	69 (36.3%)	61 (32.3%)	70 (36.8%)	200 (35.1%)
Los Angeles classification	Grade A	54 (28.4%)	54 (28.6%)	53 (27.9%)	161 (28.3%)
	Grade B	77 (40.5%)	76 (40.2%)	77 (40.5%)	230 (40.4%)
	Grade C	49 (25.8%)	50 (26.5%)	48 (25.3%)	147 (25.8%)
	Grade D	10 (5.3%)	9 (4.8%)	12 (6.3%)	31 (5.4%)

FAS: Full analysis Set. CEC: Central evaluation committee. PPS: Per-protocol set

The most common reasons for discontinuation of the study were:

- Consent withdrawn; 3, 9 and 1 in the D40, D20 and O20 group.
- Severe non-compliance to placebo; 5, 2 and 3 in the D40, D20 and O20 group.

Summary of efficacy results

The healing rates of RE at Week 8 were 90.0% in D40, 87.3% in D20 and 87.4% in O20, respectively (Table S 2). The lower limits of the 95% CIs for the difference of healing rates of RE at Week 8 were ≥ –10%. These results imply that the non-inferiorities of D40 and D20 to O20 were proven. In addition, this was also proven in other analysis sets, ie, FAS by central evaluation committee and PPS. The results of the secondary variable, the RE healing at Week 4 supported the results of the primary variable.

Table S 2 Summary of efficacy results

Healing rate (%) of RE (FAS)							
		D40	**D20**	**O20**	**Difference**		
					D40 - O20	**D20 - O20**	**D40 - D20**
Week 4	Estimate	74.2 (141/190)	77.8 (147/189)	75.3 (143/190)	-1.1	2.5	-3.6
	95% CI	67.6, 79.9	71.3, 83.1	68.7, 80.9	-9.7, 7.7	-6.0, 11.0	-12.1, 5.0
Week 8	Estimate	90.0 (171/190)	87.3 (165/189)	87.4 (166/190)	2.6	-0.1	2.7
	95% CI	84.9, 93.5	81.8, 91.3	81.9, 91.4	-3.8, 9.1	-6.9, 6.7	-3.8, 9.2

Healing rate (%) of RE at Week 4 and Week 8 by baseline LA classification (Grade A/B and C/D) (FAS)				
	LA classification	**D40**	**D20**	**O20**
Week 4	Grade A/B	77.1 (101/131)	78.5 (102/130)	80.0 (104/130)
	Grade C/D	67.8 (40/59)	76.3 (45/59)	65.0 (39/60)
Week 8	Grade A/B	90.8 (119/131)	89.2 (116/130)	91.5 (119/130)
	Grade C/D	88.1 (52/59)	83.1 (49/59)	78.3 (47/60)

Median time (days) to sustained resolution of GERD symptom			
I: A burning feeling, rising from the stomach or lower part of the chest towards the neck (FAS*)			
	D40 (n=126)	**D20 (n=100)**	**O20 (n=129)**
Estimate (95% CI)	1.0 (1.0 – 2.0)	1.5 (1.0 – 4.0)	2.0 (1.0 – 4.0)
II: Flow of sour or bitter fluid into mouth (FAS*)			
	D40 (n=110)	**D20 (n=98)**	**O20 (n=110)**
Estimate (95% CI)	1.5 (1.0 – 3.0)	3.0 (2.0 – 5.0)	3.5 (2.0 – 5.0)
III: Central upper abdominal pain (FAS*)			
	D40 (n=85)	**D20 (n=85)**	**O20 (n=85)**
Estimate (95% CI)	4.0 (1.0 – 7.0)	4.0 (2.0 – 8.0)	6.5 (4.0 – 10.0)
IV: Difficulties in swallowing (FAS*)			
	D40 (n=58)	**D20 (n=55)**	**O20 (n=64)**
Estimate (95% CI)	1.0 (1.0 – 5.0)	3.0 (1.0 – 11.0)	1.5 (1.0 – 3.0)
Median time (days) to sustained resolution of all GERD symptoms (FAS*)			
	D40 (n=155)	**D20 (n=144)**	**O20 (n=156)**
Estimate (95% CI)	8.0 (5.0 – 16.0)	9.0 (6.0 – 13.0)	10.0 (7.0 – 14.0)

CI: Confidence interval
* Subjects who had no GERD symptoms at baseline were excluded.

Summary of safety results

The frequency of reported AEs was similar between the three treatment groups, 22.1% in the D40 group, 24.9% in the D20 group, and 25.8% in the O20 group (Table S 3). The most commonly reported AEs were shown in Table S 4. In general, the differences in reporting frequency between the three 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					
	D40 (n=190)		D20 (n=189)		O20 (n=190)	
Adverse event	42	(22.1)	47	(24.9)	49	(25.8)
Serious adverse event leading to death	0		0		0	
Serious adverse event not leading to death	0		1	(0.5)	1	(0.5)
Adverse event leading to discontinuation of study treatment	1	(0.5)	3	(1.6)	4	(2.1)
Other significant adverse event [b]	0		0		0	
Related adverse event [c]	8	(4.2)	15	(7.9)	16	(8.4)
Severe adverse event	0		0		0	
	Total number of adverse events [d]					
Adverse event	56		53		61	
Serious adverse event not leading to death	0		2		1	
Adverse event leading to discontinuation of study treatment	1		3		4	
Related adverse event [c]	9		17		18	

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

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

Preferred term	D40 (n=190)		D20 (n=189)		O20 (n=190)	
Nasopharyngitis	10	(5.3)	6	(3.2)	10	(5.3)
Headache	4	(2.1)	2	(1.1)	1	(0.5)
Diarrhoea	2	(1.1)	3	(1.6)	6	(3.2)
Rash	3	(1.6)	1	(0.5)	0	
ALT increased	2	(1.1)	2	(1.1)	1	(0.5)
CPK increased	1	(0.5)	2	(1.1)	3	(1.6)
Eczema	0		3	(1.6)	0	
Rhinitis	2	(1.1)	0		0	
Constipation	2	(1.1)	0		1	(0.5)
Hepatic function abnormal	2	(1.1)	0		0	

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

Preferred term	D40 (n=190)		D20 (n=189)		O20 (n=190)	
Gastroenteritis	0		2	(1.1)	3	(1.6)
Gastritis atrophic	0		2	(1.1)	0	
Urticaria	1	(0.5)	0		2	(1.1)
Abdominal pain	0		1	(0.5)	2	(1.1)
Vertigo	0		0		2	(1.1)

A cut off of 1% has been used.
MedDRA version 11.1.
Number (%) of subjects with AEs, sorted by preferred term in decreasing order of frequency sorted by the total for both esomeprazole groups combined.

A total of 2 subjects had one or more SAEs other than death during the study; 1 each in the D20 group (influenza like illness and bronchopneumonia) and the O20 group (gastroenteritis). No SAEs were observed in the D40 group. There were no SAEs considered related to D961H by the investigators.

A total of 8 subjects were discontinued due to AEs; 1 subject in the D40 group (rash), 3 subjects in the D20 group (eczema, gastroenteritis, and asthma), and 4 subjects in the O20 group (urticaria, gastroenteritis, oesophageal candidiasis, and drug hypersensitivity).

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

Date of the report

28 May 2009