Clinical Study Report Synopsis

Drug Substance	D961H
Study Code	D961HC00006
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 once daily oral administration with omeprazole 10 mg and D961H 10 mg once daily oral administration in maintenance treatment in patients with healed reflux esophagitis

Study dates: First patient enrolled: 8 January 2008
Last patient completed: 19 May 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 61 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) for 24 weeks on maintenance of RE in patients with healed reflux esophagitis (RE) in comparison with omeprazole 10 mg once daily (O10) and D961H 10 mg once daily (D10) by assessment of presence/absence of recurrence of RE throughout the treatment period (from the randomisation to the treatment completion) according to the LA classification.

The secondary objectives of the study were as follows:

- To evaluate the efficacy of D20 on maintenance of healed RE in comparison with O10 and D10 by assessment of the presence/absence of recurrence of RE at Week 4 or before and Week 12 or before according to the LA classification.

- To evaluate the efficacy of D20 on GERD symptoms in comparison with O10 and D10 by assessment of the presence/absence and the severity of gastrointestinal investigator-reported symptoms at Week 4, 8, 12, 16, 20 and 24.

- To assess the safety and tolerability of D10, D20 and O10 in long-term administration (at Week 24) 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-3 group study on the patients with healed RE.

Target healthy volunteer population and sample size

Male and female patients aged 20 years or over, with endoscopically verified healed RE after initial treatment in the preceding study (D961HC00002), or general practice with a proton pump inhibitor (PPI).

A total of 540 subjects were to be randomised for each treatment group in the study.

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 1 tablet of omeprazole tablet placebo were orally administered once daily after breakfast for up to 24 weeks in patients randomised into the D20 group.

- D961H capsule 10 mg
  One capsule of D961H capsule 10 mg and 1 tablet of omeprazole tablet placebo were orally administered once daily after breakfast for up to 24 weeks in patients randomised into the D10 group.

Comparator, dosage and mode of administration

- Omeprazole tablet 10 mg
  One tablet of omeprazole tablet 10 mg and 1 capsule of D961H capsule placebo were orally administered once daily after breakfast for up to 24 weeks in patients randomised into the O10 group.

Duration of treatment

Up to 24 weeks.

Criteria for evaluation - efficacy and pharmacokinetics (main variables)

- **Primary outcome variable:**

  - Presence/absence of recurrence of RE throughout the treatment period according to LA classification.

- **Secondary outcome variables:**

  [Maintenance of healed RE]

  - Presence/absence of recurrence of RE at Week 4 or before and Week 12 or before according to LA classification.

  [GERD symptoms]

  - Presence/absence of each GERD symptom based on the severity assessment for 7 days before the scheduled visits at Weeks 4, 8, 12, 16, 20 and 24.

Criteria for evaluation - safety (main variables)

  - AEs

  - Laboratory test values

  - Vital signs (blood pressure, pulse rate)

Statistical methods

The endoscopically verified recurrence of RE was handled as an event. The time to event from the randomisation was analysed by Kaplan-Meier method and Kaplan-Meier plot were prepared for each treatment group. The time curve of D20 was compared to those of D10 and O10 by Log-rank test. The recurrence-free rates at Weeks 4, 12 and 24 and their two-sided 95% confidence intervals were calculated for each treatment group.

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)

		D20	D10	O10	Total
Number of subjects who were randomised		188	189	187	564
Number of subjects who completed study		160	154	148	462
Number of subjects who discontinued study		28	35	39	102
Number of subjects (%) included in Safety analysis set		188	188	187	563
Number of subjects (%) included in FAS		188	188	187	563
Number of subjects (%) included in FAS by CEC		175	178	179	532
Number of subjects (%) included in PPS		176	174	171	521
Sex	Male	142 (75.5%)	137 (72.9%)	145 (77.5%)	424 (75.3%)
	Female	46 (24.5%)	51 (27.1%)	42 (22.5%)	139 (24.7%)
Age (years)	≤64	131 (69.7%)	131 (69.7%)	137 (73.3%)	399 (70.9%)
	≥65 to ≤74	45 (23.9%)	41 (21.8%)	38 (20.3%)	124 (22.0%)
	≥75	12 (6.4%)	16 (8.5%)	12 (6.4%)	40 (7.1%)
	Mean (Standard deviation)	55.7 (13.1)	57.0 (13.3)	55.2 (13.1)	56.0 (13.1)
	Median	56.5	58.0	56.0	57.0
	Minimum – Maximum	28 - 88	21 - 93	27 - 95	21 - 95
Helicobacter pylori status	Negative	144 (76.6%)	136 (72.3%)	150 (80.2%)	430 (76.4%)
	Positive	44 (23.4%)	52 (27.7%)	37 (19.8%)	133 (23.6%)
Genotype of CYP2C19	Poor metaboliser	27 (14.4%)	30 (16.0%)	29 (15.5%)	86 (15.3%)
	Hetero extensive metaboliser	92 (48.9%)	105 (55.9%)	99 (52.9%)	296 (52.6%)
	Homo extensive metaboliser	69 (36.7%)	53 (28.2%)	59 (31.6%)	181 (32.1%)
Oesophagus hiatus hernia	Absent	61 (32.4%)	67 (35.6%)	69 (36.9%)	197 (35.0%)
	Present	127 (67.6%)	121 (64.4%)	118 (63.1%)	366 (65.0%)
Enrolment	From Study D961HC00002	153 (81.4%)	147 (78.2%)	149 (79.7%)	449 (79.8%)
	From general practice	35 (18.6%)	41 (21.8%)	38 (20.3%)	114 (20.2%)

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

The most common reasons for discontinuation of the study were:

- Recurrence; 5, 15 and 21 in the D20, D10 and O10 group.

- Consent withdrawn; 9, 6 and 11 in the D20, D10 and O10 group.

Summary of efficacy results

The efficacy results are summarised in Table S 2. The estimated recurrence-free rate of RE at Week 24, which was the primary variable, was statistically significantly higher in the D20 group compared to the O10 group (92.0% for D20 and 82.7% for O10, p=0.007, Log-rank test). In the comparison of the estimated recurrence-free rate of RE at Week 24 between D20 and D10, the value in D20 was numerically higher than in D10, but there was no statistically significant difference (92.0% for D20 and 87.5% for D10, p=0.158, Log-rank test). The order

of the estimated recurrence-free rates of RE at Weeks 4 and 12 was same as the order at Week 24. The results in the FAS by CEC and the PPS were similar to those in the FAS.

Table S 2   Summary of efficacy results

Estimated recurrence-free rates of RE by Kaplan-Meier method (FAS)

		D20 (n=188)	D10 (n=188)	O10 (n=187)
Week 4	Estimated rate	97.8	95.7	91.4
	95% CI	95.7, 99.9	92.7, 98.6	87.3, 95.4
Week 12	Estimated rate	95.0	91.1	86.8
	95% CI	91.8, 98.2	86.9, 95.3	81.9, 91.8
Week 24	Estimated rate	92.0	87.5	82.7
	95% CI	88.0, 96.0	82.7, 92.4	77.2, 88.3
–	Log-rank test (vs D10)	p=0.158	–	–
	Log-rank test (vs O10)	p=0.007	–	–

Observed recurrence-free rates of RE (FAS)

		D20 (n=188)	D10 (n=188)	O10 (n=187)
Week 4	Observed rate	97.9 (184/188)	95.7 (180/188)	91.4 (171/187)
	95% CI	94.7, 99.2	91.8, 97.8	86.6, 94.7
	Chi-square test (vs D10)	p=0.241	–	–
	Chi-square test (vs O10)	p=0.006	–	–
Week 12	Observed rate	95.2 (179/188)	91.5 (172/188)	87.2 (163/187)
	95% CI	91.2, 97.5	86.6, 94.7	81.6, 91.2
	Chi-square test (vs D10)	p=0.147	–	–
	Chi-square test (vs O10)	p=0.006	–	–
Week 24	Observed rate	92.6 (174/188)	88.3 (166/188)	83.4 (156/187)
	95% CI	87.9, 95.5	82.9, 92.1	77.4, 88.1
	Chi-square test (vs D10)	p=0.161	–	–
	Chi-square test (vs O10)	p=0.007	–	–

Shift table showing absence/presence of GERD symptoms at the last visit against baseline (FAS[*])

		D20		D10		O10	
		Baseline		Baseline		Baseline	
		Absence	Presence	Absence	Presence	Absence	Presence
Heartburn	Absence	96.6 (141/146)	85.4 (35/41)	95.1 (156/164)	90.5 (19/21)	95.1 (155/163)	65.2 (15/23)
	Presence	3.4 (5/146)	14.6 (6/41)	4.9 (8/164)	9.5 (2/21)	4.9 (8/163)	34.8 (8/23)
Acid regurgitation	Absence	95.5 (147/154)	81.8 (27/33)	96.9 (157/162)	73.9 (17/23)	93.7 (149/159)	70.4 (19/27)
	Presence	4.5 (7/154)	18.2 (6/33)	3.1 (5/162)	26.1 (6/23)	6.3 (10/159)	29.6 (8/27)
Epigastric pain	Absence	94.2 (131/139)	75.0 (36/48)	94.2 (147/156)	72.4 (21/29)	97.3 (145/149)	73.0 (27/37)
	Presence	5.8 (8/139)	25.0 (12/48)	5.8 (9/156)	27.6 (8/29)	2.7 (4/149)	27.0 (10/37)
Dysphagia	Absence	97.6 (160/164)	82.6 (19/23)	98.8 (168/170)	86.7 (13/15)	97.1 (166/171)	60.0 (9/15)
	Presence	2.4 (4/164)	17.4 (4/23)	1.2 (2/170)	13.3 (2/15)	2.9 (5/171)	40.0 (6/15)

CI: Confidence interval.

In case of estimated recurrence-free rate, CI was calculated by Greenwood formula (which is very crude for small samples, in particular when the estimate is 100%).

In case of observed recurrence-free rate, CI was calculated by Newcombe-Wilson score method.

[*] Subjects with a measurement at baseline and at least 1 subsequent variable measurement.

Summary of safety results

The frequencies of reported AEs in the D20 and D10 group were similar, but numerically higher compared to that one in the O10 group (60.1%, 58.0%, 48.1% in the D20, D10 and O10 group, respectively) (Table S 3). The most commonly reported AEs were shown in Table S 4. In general, the numerical differences in reporting frequency between the three treatment groups were 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					
	D20 (n=188)		D10 (n=188)		O10 (n=187)	
Adverse event	113	(60.1)	109	(58.0)	90	(48.1)
Serious adverse event leading to death	0		0		0	
Serious adverse event not leading to death	5	(2.7)	4	(2.1)	1	(0.5)
Adverse event leading to discontinuation of study treatment	6	(3.2)	9	(4.8)	3	(1.6)
Other significant adverse event [b]	0		0		0	
Related adverse event [c]	17	(9.0)	15	(8.0)	10	(5.3)
Severe adverse event	2	(1.1)	1	(0.5)	0	
	Total number of adverse events [d]					
Adverse event	207		202		182	
Serious adverse event not leading to death	5		4		1	
Adverse event leading to discontinuation of study treatment	6		9		6	
Related adverse event [c]	20		15		15	
Severe adverse event	2		1		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: 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	D20 (n=188)		D10 (n=188)		O10 (n=187)	
Nasopharyngitis	31	(16.5)	37	(19.7)	31	(16.6)
Abdominal pain upper	11	(5.9)	3	(1.6)	4	(2.1)
Diarrhoea	4	(2.1)	7	(3.7)	7	(3.7)
Blood creatine phosphokinase increased	5	(2.7)	5	(2.7)	2	(1.1)
Gastric polyps	3	(1.6)	4	(2.1)	1	(0.5)
Cough	3	(1.6)	4	(2.1)	1	(0.5)
Blood pressure increased	1	(0.5)	5	(2.7)	1	(0.5)
Contusion	5	(2.7)	0		2	(1.1)
Upper respiratory tract infection	4	(2.1)	1	(0.5)	0	

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

Preferred term	D20 (n=188)		D10 (n=188)		O10 (n=187)	
Gastrooesophageal reflux disease	2	(1.1)	2	(1.1)	5	(2.7)
Constipation	2	(1.1)	1	(0.5)	4	(2.1)
Abdominal distension	0		0		4	(2.1)

A cut off of 2% 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 10 subjects reported one or more SAEs other than death during the study. The total frequency of reported SAEs were numerically higher in the D20 and D10 groups compared to the O10 group, however, there were only single occurrences by preferred term and no safety concerns were raised.

A total of 18 subjects discontinued the study due to AEs. The total frequency of reported DAEs were numerically higher in the D20 and D10 groups compared to the O10 roup, however, there were only single occurrences by preferred term and no safety concerns were raised.

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 September 2009