Clinical Study Report Synopsis

Drug Substance D961H

Study Code D961UC00002

Edition Number 1

A Multicentre, Randomised, Double-Blind, Parallel-Group, Comparative Study to Compare the Efficacy and Safety of D961H 20 mg Twice Daily Oral Administration and D961H 20 mg Once Daily Oral Administration in Patients With Refractory Reflux Esophagitis

Study dates: First patient enrolled: 25 August 2012
Last patient last visit: 30 May 2014

Phase of development: Therapeutic confirmatory (III)

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

This document contains trade secrets and confidential commercial information, disclosure of which is prohibited without providing advance notice to AstraZeneca and opportunity to object.

Publications

None at the time of writing this report.

Objectives and criteria for evaluation

The objectives and outcome variables are provided in Table S1.

Table S1 Objectives and outcome variables

Objective			Outcome Variable
Priority	**Type**	**Description**	**Description**
Primary	Efficacy	To evaluate the efficacy of D20 bid on healing of refractory RE in comparison with D20 qd at Week 8	Presence/absence of RE according to the LA classification at Week 8
Secondary	Efficacy	To evaluate the efficacy of D20 bid on healing of RE in comparison with D20 qd at Week 4	Presence/absence of RE according to the LA classification at Week 4
	PRO	To evaluate the efficacy of D20 bid on GERD symptoms in comparison with D20 qd	Presence/absence and severity of the patient-reported symptoms: Time to sustained resolution of individual GERD symptom (during Visit 3 [Week 4] and Visit 4 [Week 8]) Proportion of patients with sustained resolution of individual GERD symptoms during Week 1 (Day 1 to 7), Week 2 (Day 8 to 14), and during Week 4 and Week 8 (7 days preceding Visit 3 [Week 4] and Visit 4 [Week 8]) Number of days with individual GERD symptoms during Week 1 (Day 1 to 7), Week 2 (Day 8 to 14), and during Week 4 and Week 8 (7 days preceding Visit 3 [Week 4] and Visit 4 [Week 8]) Maximum severity (none, mild, moderate, severe, and missing) of individual GERD symptoms during Week 1 (Day 1 to 7), Week 2 (Day 8 to 14), and during Week 4 and Week 8 (7 days preceding Visit 3 [Week 4] and Visit 4 [Week 8])
	Safety	To evaluate the safety and tolerability of D20 bid and D20 qd	Assessment of AEs, laboratory test values (clinical chemistry, haematology, and urinalysis) and vital signs (body temperature, blood pressure and pulse rate)

AE Adverse events; bid Twice daily; GERD Gastroesophageal reflux disease; LA Los Angeles; PRO Patient reported outcome; qd Once daily; RE Reflux esophagitis.

Study design

This was a Phase III, multicentre, randomised, double-blind, parallel-group comparative study to evaluate the efficacy and safety of D961H 20 mg twice daily (D20 bid) and D961H 20 mg once daily (D20 qd) in patients with refractory reflux esophagitis (RE).

Eligible patients were randomised in a 1:1 ratio to receive either D20 bid or D20 qd for a maximum duration of 8 weeks.

Target subject population and sample size

Male and female patients aged ≥20 years, with RE verified by esophagogastroduodenoscopy (EGD) and classified into Los Angeles (LA) Classification Grades A, B, C, or D within 1 week prior to randomisation into the study despite of at least 8-week treatment with the standard doses of proton-pump inhibitors (PPIs) (omeprazole 20 mg qd, esomeprazole 20 mg qd, lansoprazole 30 mg qd or rabeprazole sodium 10 mg qd and 20 mg qd).

A total of 280 patients (140 patients per treatment group), including at least 20 patients with Grade C or D RE, were planned to be randomised.

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

The investigational products used in this study were D961H capsules 20 mg (batch number: 12-001037AZ) and D961H capsules 20 mg placebo (batch number: 12-001107AZ). One D961H capsule was orally administered bid (one capsule in the morning after breakfast and in the evening after dinner) for a maximum of 8 weeks in patients randomised to D20 bid, whereas patients randomised to D20 qd received 1 D961H capsule 20 mg in the morning and 1 D961H capsule 20 mg placebo in the evening.

Duration of treatment

Duration of the treatment was a maximum of 8 weeks. Patients who healed at Week 4 completed the study at that point in time.

Statistical methods

Primary variable

The healing rate of RE at Week 8 and its 2-sided 95% Confidence Interval (CI) was calculated for each treatment group using the Newcombe-Wilson score method without continuity correction. The difference in healing rates and the 2-sided 95% CI between D20 bid group and D20 qd group was obtained using the Newcombe-Wilson score method without continuity correction. The healing rates of RE at Week 8 was compared between D20 bid group and D20 qd group based on a chi-square test. The healing rates at Week 8 was also compared between D20 bid group and D20 qd group using Cochran-Mantel-Haenszel test stratified by the baseline LA classification, CYP2C19 genotype, and pre-treatment of PPI among other subgroups. These analyses were secondary so the multiplicity of these tests was not adjusted.

In addition, the Kaplan-Meier method was used to analyse time from the randomisation to the confirmed day of healed RE and to estimate the time-to-event curves for healing of RE for D20 bid and D20 qd groups.

Both the Full Analysis Set (FAS) and the Per Protocol Analysis Set (PPS) were used for the analyses of the primary variable. The primary analysis was based on the FAS. In addition, the secondary analysis for the primary variable was done using FAS by Central Evaluation Committee (CEC).

Secondary variables

The healing rate of RE at Week 4 was analysed in line with the analysis of the primary variable. The time to sustained resolution (number of days from the randomisation up to the first day of 7 consecutive days free of that symptom) of each Gastroesophageal Reflux Disease (GERD) symptom was analysed by the Kaplan-Meier method. The proportions of patients with sustained resolution at Weeks 1, 2, and 4 out of the subset of the FAS who had the corresponding GERD symptom at baseline were obtained for each treatment group together with the 95% CIs calculated by the Newcombe-Wilson score method without continuity correction.

For safety variables, data were summarised using descriptive statistics for each treatment group in the safety analysis set.

Subject population

The patient population in this study well reflected the target population. The treatment groups were well-balanced with respect to the demographic and baseline characteristics.

A total of 1398 patients were enrolled in the screening period and 287 (20.5%) patients were randomised to treatment (145 [10.4%] and 142 [10.2%] patients in the D20 bid and D20 qd groups, respectively). Out of the randomised patients, there were 46 (16.1%) patients who had LA classification Grades C/D at baseline. A total of 14 (4.9%) patients discontinued the study and the most common reason for discontinuation was AEs (2 [1.4%]) patients in D20 bid and 6 (4.2%) patients in the D20 qd groups).

The demographic and baseline characteristics of the FAS by CEC and PPS were similar to those of the FAS.

Summary of efficacy results

Primary variable: Healing rate (%) of RE by LA classification at Week 8

The primary efficacy variable was defined as the proportion of patients with healed RE verified by EGD during the study treatment (by Week 8). Healing rates (%) of RE at Week 8 and Week 4 in the FAS are summarised in Table S2.

The healing rate of RE at Week 8 in D20 bid group was statistically significantly higher than that in D20 qd group (92.4% versus 68.6%, p-value <0.0001). D20 bid was superior to D20 qd for healing of refractory RE at Week 8.

The cumulative healing rates of RE at Week 8 were consistent with the primary result.

Healing rates of RE for D20 bid group were higher than D20 qd group for all subgroups.

The results in the FAS by CEC and PPS were similar to those in the FAS.

Table S2 Healing rates (%) of RE at Week 4 and Week 8 (Full analysis set)

Variable	Type of estimate	D20 bid (N=145)	D20 qd (N=140)	Difference between groups
Healing Rate (%) of RE at Week 4	Estimate	118(81.4)	68(48.6)	32.8
	95% CI	(74.3, 86.9)	(40.4, 56.8)	(21.9, 42.6)
	P-value (Chi-square test)			<0.0001
Healing Rate (%) of RE at Week 8	Estimate	134(92.4)	96(68.6)	23.8
	95% CI	(86.9, 95.7)	(60.5, 75.7)	(14.9, 32.6)
	P-value (Chi-square test)			<0.0001

The two-sided 95% CIs for healing rates of RE at Week 4 and Week 8 and for the differences of healing rates of RE were calculated by the Newcombe-Wilson score method without continuity correction.
Percentages were calculated based on the actual patients considered for analysis.
bid Twice daily; CI Confidence interval; N Number of patients in treatment group; qd Once daily; RE Reflux esophagitis.

Secondary variable: Healing rate (%) of RE at Week 4

The healing rates at Week 4 in D20 bid group was statistically significantly higher than that in D20 qd group (81.4% versus 48.6%, p−value <0.0001) (Table S2). The results of healing rate of RE at Week 4 were well consistent with those at Week 8.

Secondary variable: Presence/absence of patient-reported GERD symptom

At Week 4, a numerically higher proportion of patients treated with D20 bid experienced early resolution of heartburn and acid regurgitation compared to D20 qd and the median time to sustained resolution of individual symptoms was numerically shorter in D20 bid compared to D20 qd groups; however, these differences were not statistically significant. Other GERD symptoms (abdominal pain, difficulty in swallowing, and sleep disturbance) showed similar results as heartburn and acid regurgitation.

Summary of safety results

The overall safety results showed that there were no safety or tolerability concerns identified in this study. The safety profile observed in this study was similar to existing safety data in Japan/rest of the world.

The mean duration of exposure in D20 bid group (32.8 days, range: 7 days to 60 days) was shorter than in D20 qd group (40.7 days, range: 3 days to 64 days). The shorter duration of exposure in the D20 bid group could be explained by the high healing rates of RE at Week 4.

A total of 35 Adverse Events (AEs) were reported by 26 (17.9%) patients in the D20 bid group and 61 AEs were reported by 43 (30.3%) patients in the D20 qd group. The numerically higher frequency of reported AEs in the D20 qd group could be driven by the longer exposure time compared to the D20 bid group. There were no deaths reported in this study. The number of patients with any serious adverse events was 1 (0.7%) in the D20 bid group and 3 (2.1%) patients in the D20 qd group. A total of 2 (1.4%) patients in the D20 bid and 6 (4.2%) patients in the D20 qd groups discontinued the study treatment due to AEs.

The System Organ Class (SOC) in which most patients reported AEs was infections and infestations (9 [6.2%] and 17 [12%] patients in the D20 bid and D20 qd groups, respectively). The Preferred Term (PT) in which most patients reported AEs was nasopharyngitis (8 [5.5%] and 9 [6.3%] patients in the D20 bid and D20 qd groups, respectively).

There were no clinically relevant trends found in the 2 treatment groups regarding clinical laboratory values and vital signs.