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COMPOUND NUMBER: CJ-040,714

PROTOCOL NO: A7421007

PROTOCOL TITLE: A Randomized, Double Blind, Parallel Group Study to Examine the Effect of Multiple Doses of CJ-040,714 on Distal Esophageal Acid Exposure in Patients With Erosive Gastro-Esophageal Reflux Disease (GERD)

Study Centers: Two (2) centers 1 in the United Kingdom (UK) and 1 in Belgium took part in the study and randomized subjects.

Study Initiation and Final Completion Dates: 14 December 2005 to 20 February 2007

Phase of Development: Phase 2

Study Objectives:

Primary Objective:

- To investigate the effect of CJ-040,714 on the fraction of time that esophageal pH was < 4

Secondary Objectives:

- To investigate the effect of CJ-040,714 on the duration of the longest acid reflux event
- To investigate the effect of CJ-040,714 on the number of acid reflux events
- To investigate the effect of CJ-040,714 on the number of acid reflux events >5 minutes in length
- To investigate the effect of CJ-040,714 on the esophageal clearance time of acid reflux events
- To investigate the pharmacokinetic (PK)/pharmacodynamics (PD) relationship with regards to the primary endpoint
- To investigate the effect of CJ-040,714 on the mean duration of acid reflux events

All subjects were planned to be assessed for upright, supine, day time and night time reflux events however, the primary focus of interest was total (defined by upright and supine) events.

METHODS

Study Design: This was a randomized, double blind, parallel group study to investigate the effect of 7 days of dosing of CJ-040,714 on the distal esophageal acid exposure in 24 subjects with erosive GERD. Subjects were randomized to receive 1 of 2 doses of CJ-040,714 (5 mg once daily [OD] or 20 mg twice daily [BID]) for a total of 7 days.

For each subject, the study comprised a screening visit, 2 visits to have a pH catheter inserted into the esophagus (once at Baseline and once after 7 days of dosing), a visit to commence dosing (Day 1), and a Follow-up Visit approximately 14 days after the last dose of study drug. Subjects were resident in the study center for the duration of the 24 hour pHmetry recording at Baseline and also for 24 hours on Day 7 for a further pHmetry recording. Study procedures are summarized in Table 1.

Table 1. Overview of Study Procedures

Procedure	Visit						
	Screening	Baseline		Day 1	Day 7[a]	Day 8	Follow-Up
		Day 1[a]	Day 2				
Informed consent	X						
Medical history[b]	X						
Alcohol breath/urine test	X	X		X[c]			
Prior/concomitant medication	X----------	----------	----------	----------	----------	----------	----------X
Physical examination	X			X[c]		X	X
Safety laboratory tests[d]	X						X
Drugs of abuse testing	X						
12-lead electrocardiogram	X			X[e]		X	X
Vital signs[f]	X	X[g]	X	X[e]	X[g]	X	X
Genotyping				X[c]			
Pharmacokinetic blood sample				X[e]	X[g]	X	
pHmetry start		X[h]			X[i]		
pHmetry stop			X			X	
Dosing CJ-040,714[j]				X----------	----------X		
Rescue medication taken		X----------	----------	----------	----------	----------	----------X
Adverse event assessment		X----------	----------	----------	----------	----------	----------X
Resident in study centre		X----------	----------X		X----------	----------X	

a. Following an overnight fast.
b. Including drug, alcohol and tobacco use.
c. Performed prior to dosing.
d. Laboratory safety tests included clinical chemistry, hematology and urinalysis. At Screening this also included virology and a follicle stimulating hormone test for female subjects.
e. Premorning dose and at 2 hours postmorning dose.
f. Supine and standing blood pressure (systolic and diastolic) and pulse rate.
g. Premorning dose and at 2, 6 and 12 hours postmorning dose (at Baseline this was post pH catheter placement).
h. If the pHmetry test failed due to a technical fault it was to be repeated prior to entry into the study.
i. If the pHmetry test failed due to a technical fault it was to be repeated on Day 8, 9 or 10.
j. Dosing CJ-040,714 took place at the study center on Days 1 (morning dose) and 7, and on an out-patient basis at all other times. If the Day 7 pH test required a repeat, dosing of CJ-040,714 was to be continued until the day of testing.

Number of Subjects (Planned and Analyzed): The plan for this study was to enroll 24 subjects. A total of 24 subjects (11 in the UK and 13 in Belgium) were screened and randomized to study treatment. Twelve (12) subjects received CJ-040,714 5 mg OD and 12 subjects received CJ-040,714 20 mg BID.

Diagnosis and Main Criteria for Inclusion: Male or female subjects aged 18 to 70 years, with a previous diagnosis of GERD by positive upper gastrointestinal endoscopy (Los Angeles Grade A, B or C) within 5 years of screening and a positive baseline pHmetry assessment. Subjects with body mass index of approximately 18 to 32 kg/m^2; and a total body weight within the range of 40 to 120 kg were included in the study.

Exclusion Criteria: Subjects with a history of significant cardiovascular disease, previously diagnosed renal and hepatic impairment, with a resting blood pressure >170/110 mmHg or <90/50 mmHg were excluded from the study.

Study Treatment: Study treatment, CJ-040,714 was provided (formulated as a hemi-edisylate salt) as 5 mg and 10 mg tablets, with matching placebo tablets (used to maintain the blinding of the study). Subjects in the 5 mg OD treatment group received 1 x 5 mg tablet of CJ-040,714 and 2 placebo tablets in the morning, and 3 placebo tablets in the evening, while subjects in the 20 mg BID treatment group received 2 x 10 mg tablets of CJ-040,714 and 1 placebo tablet both in the morning and in the evening.

Subjects received CJ-040,714 either 5 mg OD or 20 mg BID for 7 days. Each dose was administered orally with approximately 240 mL of water. On Day 7, subjects were instructed not to take study drug until they had been admitted to the study center.

Pharmacokinetic and Pharmacodynamic Endpoints:

All endpoints were calculated for upright, supine, daytime and night-time reflux events, however the primary focus of interest was total (defined by upright + supine) events.

Primary Endpoint:

- Fraction of time pH <4

Secondary Endpoints:

- Duration of longest acid reflux event
- Number of acid reflux events
- Number of acid reflux events >5 min
- Esophageal clearance of acid reflux (min/episodes)
- Mean duration of acid reflux events

No efficacy evaluations were performed for this study.

Safety Evaluations: Adverse event (AE) recording, physical examinations, laboratory tests, vital signs, blood pressure monitoring, and 12-lead electrocardiograms were performed at specified intervals throughout the study.

Statistical Methods:

Analysis Set: One (1) analysis set was used for the PD population; the Per Protocol analysis set. This consisted of all randomized subjects who met the following criteria:

- Received at least 1 dose of study drug
- Having no major violations in the planned trial following clinical review and prior to database release
- Provided a postdose pHmetry reading

Analysis Methods:

The primary endpoint, fraction (%) of time that esophageal pH was <4 was log transformed and analysed by analysis of variance (ANOVA) with the fixed effect terms for dose, time (baseline and Day 7), the time by dose interaction and subjects. Subjects with a value of 0 had their response imputed as log (0.5). Individuals had to have both baseline and Day 7 data to be included in the statistical analysis.

The contrasts of interest were:

- CJ-040,714 5 mg OD Day 7 versus Baseline
- CJ-040,714 20 mg BID Day 7 versus Baseline

No formal statistical comparison was made between the 2 doses as the study was only powered to detect differences between postdose and baseline.

The secondary endpoints; duration of longest acid reflux event, esophageal clearance of acid reflux and mean duration of acid reflux were analyzed in an identical manner as for the primary endpoint except that subjects with a 0 value had their response imputed as log (0.02). The other endpoints; number of acid reflux events and the number of acid reflux events >5 minutes were analyzed using Poisson regression with fixed effects for dose, time, dose*time and subjects.

All endpoints were analyzed using the PD analysis set. Differences between treatment means, standard errors associated with these differences, and 95% confidence intervals (CIs) for the differences were presented on the log scale. The ratios between the geometric means and the 95% CIs for these ratios were also presented.

Safety data were clinically reviewed and evaluated using descriptive statistics.

RESULTS

Subject Disposition and Demography: A total of 24 subjects were screened and randomized to study treatment. Twelve (12) subjects received CJ-040,714 5 mg OD and 12 subjects received CJ-040,714 20 mg BID. The summary of the evaluation groups are presented in Table 2. One (1) subject in each treatment group was excluded from the PD analyses. One (1) subject, in the CJ-040,714 5 mg OD treatment group, was believed to have had a hiatus hernia which caused an extremely high baseline measurement. During the postdose assessment, the pH probe also moved and therefore this reading was not considered to be a valid measurement. Another subject, in the CJ-040,714 20 mg BID treatment group, the pH probe failed during the postdose assessment and therefore no postdose reading was available for this subject.

Table 2. Subject Evaluation Groups

Number of Subjects	CJ-040,714 5 mg OD N=12	CJ-040,714 20 mg BID N=12
Treated	12	12
Completed	12	12
Discontinued	0	0
Analyzed for pharmacokinetics	12	12
Analyzed for pharmacodynamics[a]	11	11
Analyzed for safety		
Adverse events	12	12
Laboratory data[b]	10	5

BID = twice daily; N = total number of subjects; OD = once daily.
a. One subject in each treatment group was excluded from the pharmacodynamic analyses.
b. The n value for laboratory data was low because a number of subjects had their final follow-up visit outside of the laboratory test window (>21 days).

Males accounted for approximately 79% of the study population. The majority of subjects were aged between 18 and 64 years and the mean ages were similar for both treatment groups. All subjects were White with the exception of 1 subject in the CJ-040,714 20 mg BID treatment group, who was Asian. Demographic characteristics were similar for each treatment group, which are summarized in Table 3.

Table 3. Demographic Characteristics

	CJ-040,714 5 mg OD			CJ-040,714 20 mg BID		
	Male	Female	All	Male	Female	All
Number of subjects	11	1	12	8	4	12
Age (years)*	47 (31-69)	62 (62-62)	48 (31-69)	45 (27-66)	58 (52-67)	49 (27-67)
Body mass index (kg/m^2)*	27 (21-40)	32 (32-32)	27 (21-40)	29 (24-31)	31 (25-43)	29 (24-43)
Race						
White	11	1	12	7	4	11
Asian	0	0	0	1	0	1

*Values presented are the mean (range).
BID = twice daily; OD = once daily.

Pharmacokinetic and Pharmacodynamics Results:

- Fraction of time pH <4:

For subjects in the CJ-040,714 5 mg OD treatment group, the total fraction (%) of time that esophageal pH was <4 was statistically significantly less at the end of treatment than at Baseline (p=0.0111). The results for individual and mean values fraction (%) of time that esophageal pH was <4 are summarized in Table 4.

Table 4. Summary of Fraction (%) of Time that Esophageal pH was <4

	CJ-040,714 5 mg OD N=11	CJ-040,714 20 mg BID N=11
Total Over 24 Hours		
Baseline	10.48 (6.72)	13.04 (11.07)
End of treatment value	8.59 (11.04)	13.57 (11.29)
Change from Baseline	-1.89 (6.13)	0.53 (3.59)
Day Time		
Baseline	12.35 (9.21)	16.98 (15.43)
End of treatment value	11.46 (13.64)	18.11 (15.19)
Change from Baseline	-0.89 (6.45)	1.14 (7.18)
Night Time		
Baseline	6.77 (9.81)	5.14 (4.81)
End of treatment value	2.91 (6.70)	4.32 (5.02)
Change from Baseline	-3.86 (11.13)	-0.82 (6.14)

Values are arithmetic means (SD).
BID = twice daily; N = total number of subjects; OD = once daily; SD = standard deviation.

Results of the ANOVA (end of treatment versus baseline) for the fraction (%) of time that pH was <4 are summarized in Table 5.

Table 5. Summary of Statistical Analysis for Fraction (%) of Time That Esophageal pH was <4

Treatment Group	Geometric Mean Ratio*	95% CI*	p-Value
CJ-040,714 5 mg OD	0.558	0.3608, 0.8616	0.0111
CJ-040,714 20 mg BID	1.037	0.6708, 1.6020	0.8649

*The geometric mean ratio and the corresponding CIs are back transformed from the log scale.
BID = twice daily; CI = confidence interval; OD = once daily.

- Duration of Longest Acid Reflux Event:

Individual and mean values for the duration of longest acid reflux event are provided by treatment in Table 6.

Table 6. Summary of Duration of Longest Acid Reflux Event (Minutes)

	CJ-040,714 5 mg OD N=11	CJ-040,714 20 mg BID N=11
Total		
Baseline	12.12 (13.30)	15.52 (12.25)
End of treatment value	12.76 (16.70)	15.53 (7.88)
Change from Baseline	0.64 (8.73)	0.00 (12.36)
Day Time		
Baseline	11.70 (13.59)	12.09 (8.77)
End of treatment value	12.06 (16.82)	14.76 (7.89)
Change from Baseline	0.36 (8.72)	2.67 (7.26)
Night Time		
Baseline	3.57 (3.11)	8.58 (12.27)
End of treatment value	5.16 (9.35)	8.89 (8.71)
Change from Baseline	1.59 (7.84)	0.31 (16.29)

Values are arithmetic means (SD).
BID = twice daily; N = total number of subjects; OD = once daily; SD = standard deviation.

Results of the ANOVA (end of treatment versus baseline) for the duration of longest acid reflux event are summarized in Table 7.

Table 7. Summary of Statistical Analysis for the Duration of Longest Acid Reflux Event (Minutes)

Treatment Group	Geometric Mean Ratio*	95% CI*	p-Value
CJ-040,714 5 mg OD	0.592	0.2163, 1.6185	0.2896
CJ-040,714 20 mg BID	1.111	0.4062, 3.0394	0.8293

*The geometric mean ratio and the corresponding CIs are back transformed from the log scale.
BID = twice daily; CI = confidence interval; OD = once daily.

- Number of Acid Reflux Events:

Individual and mean values for the number of acid reflux events are provided by treatment in in Table 8.

Table 8. Summary of Number of Acid Reflux Events

	CJ-040,714 5 mg OD N=11	CJ-040,714 20 mg BID N=11
Total		
Baseline	166 (119, 1111)	211 (97, 544)
End of treatment value	115 (0, 366)	216 (71, 530)
Change from Baseline	-46 (-1058, 151)	4 (-140, 78)
Day Time		
Baseline	146 (113, 317)	184 (95, 495)
End of treatment value	113 (0, 290)	209 (59, 482)
Change from Baseline	-18 (-264, 105)	6 (-123, 100)
Night Time		
Baseline	20 (2, 794)	29 (0, 59)
End of treatment value	6 (0, 76)	12 (0, 48)
Change from Baseline	-12 (-794, 46)	-17 (-22, 11)

Values are median (minimum, maximum).
BID = twice daily; N = total number of subjects; OD = once daily.

Results of the ANOVA (end of treatment versus baseline) for the number of acid reflux events are summarised in Table 9.

Table 9. Summary of Statistical Analysis for the Number of Acid Reflux Events

Treatment Group	Geometric Mean Ratio*	95% CI*	p-Value
CJ-040,714 5 mg OD	0.521	0.3219, 0.8422	0.0078
CJ-040,714 20 mg BID	0.982	0.6575, 1.4670	0.9298

*The geometric mean ratio and the corresponding CIs are back transformed from the log scale.
BID = twice daily; CI = confidence interval; OD = once daily.

- Number of Acid Reflux Events >5 Minutes:

Individual and mean values for the number of acid reflux events >5 minutes are provided by treatment in Table 10.

Table 10. Summary of Number of Acid Reflux Events >5 Minutes

	CJ-040,714 5 mg OD N=11	CJ-040,714 20 mg BID N=11
Total		
Baseline	2 (0, 15)	3 (0, 27)
End of treatment value	1 (0, 21)	6 (0, 26)
Change from Baseline	0 (-9, 6)	0 (-5, 13)
Day Time		
Baseline	2 (0, 12)	2 (0, 25)
End of treatment value	1 (0, 16)	3 (0, 23)
Change from Baseline	0 (-7, 5)	0 (-4, 15)
Night Time		
Baseline	0 (0, 3)	0 (0, 2)
End of treatment value	0 (0, 5)	0 (0, 3)
Change from Baseline	0 (-2, 2)	0 (-2, 3)

Values are median (minimum, maximum).
BID = twice daily; N = total number of subjects; OD = once daily.

Results of the ANOVA (end of treatment versus baseline) for the number of acid reflux events >5 minutes are summarised in Table 11.

Table 11. Summary of Statistical Analysis for the Number of Acid Reflux Events >5 Minutes

Treatment Group	Geometric Mean Ratio*	95% CI*	p-Value
CJ-040,714 5 mg OD	0.903	0.5485, 1.4874	0.6892
CJ-040,714 20 mg BID	1.202	0.8095, 1.7834	0.3622

*The geometric mean ratio and the corresponding CIs are back transformed from the log scale.
BID = twice daily; CI = confidence interval; OD = once daily.

- Oesophageal Clearance of Acid Reflux:

Individual and mean values for the esophageal clearance of acid reflux are provided by treatment in Table 12.

Table 12. Summary of Clearance of Acid Reflux (Minutes)

	CJ-040,714 5 mg OD N=11	CJ-040,714 20 mg BID N=11
Total		
Baseline	0.77 (0.44)	0.71 (0.31)
End of treatment value	0.69 (0.40)	0.81 (0.35)
Change from Baseline	-0.08 (0.36)	0.10 (0.35)
Day Time		
Baseline	0.77 (0.48)	0.67 (0.33)
End of treatment value	0.69 (0.41)	0.75 (0.28)
Change from Baseline	-0.08 (0.38)	0.08 (0.28)
Night Time		
Baseline	0.61 (0.47)	0.75 (0.65)
End of treatment value	0.59 (0.57)	1.24 (1.67)
Change from Baseline	-0.02 (0.51)	0.49 (1.96)

Values are arithmetic means (SD).
BID = twice daily; N = total number of subjects; OD = once daily; SD = standard deviation.

Results of the ANOVA (end of treatment versus baseline) for the clearance of acid reflux are summarised in Table 13.

Table 13. Summary of Statistical Analysis for the Clearance of Acid Reflux (Minutes)

Treatment Group	Geometric Mean Ratio*	95% CI*	p-value
CJ-040,714 5 mg OD	0.767	0.4316, 1.3641	0.3484
CJ-040,714 20 mg BID	1.140	0.6413, 2.0273	0.6394

*The geometric mean ratio and the corresponding CIs are back transformed from the log scale.
BID = twice daily; CI = confidence interval; OD = once daily

- Mean Duration of Acid Reflux Events:

The mean duration of acid reflux events is a duplication of the previous endpoint; esophageal clearance of acid reflux and the results are identical for the 2 endpoints.

Safety Results: Table 14 summarises the number of subjects reporting at least 1 AE, the overall number of AEs reported, and the individual events reported, for treatment emergent all causality and treatment related AEs. The proportion of subjects reporting all causality AEs was similar in both treatment groups.

The most frequently reported AEs were diarrhea and headache, in both treatment groups. All AEs were considered to be related to the study drug with the exception of 3 events; pharyngolaryngeal discomfort in the CJ-040,714 5 mg OD treatment group, and dyspepsia and a foot fracture in the CJ-040,714 20 mg BID treatment group.

Table 14. Treatment Emergent Adverse Events

Number of Subjects With[a]	CJ-040,714 5 mg OD N=12	CJ-040,714 20 mg BID N=12
Number of subjects with ≥1 adverse event	10 (10)	9 (9)
Number of adverse events reported	23 (22)	18 (16)
Diarrhoea	8 (8)	6 (6)
Headache	4 (4)	3 (3)
Abdominal discomfort	1 (1)	2 (2)
Constipation	2 (2)	0
Hot flush	0	2 (2)
Abdominal distension	1 (1)	0
Eructation	0	1 (1)
Mucous stools	1 (1)	0
Influenza	0	1 (1)
Pain in extremity	1 (1)	0
Sensation of heaviness	0	1 (1)
Dizziness	1 (1)	0
Head discomfort	1 (1)	0
Sedation	1 (1)	0
Eczema	1 (1)	0
Dyspepsia	0	1 (0)
Foot fracture	0	1 (0)
Pharyngolaryngeal discomfort	1 (0)	0

BID = twice daily; N = total number of subjects; OD = once daily.
a. The numbers shown were for all causality events (treatment related adverse events).

There were no serious AEs (SAEs), discontinuations due to AEs, or deaths in this study.

There were no laboratory test abnormalities that were considered to be clinically significant.

CONCLUSIONS: There was a statistically significant (p=0.0111) reduction in 24 hour esophageal acid exposure in subjects who received CJ-040,714 5 mg OD. Conversely, there was no evidence to suggest that CJ-040,714 20 mg BID reduced the fraction of time that esophageal pH was <4 in subjects with erosive GERD (p=0.8649). The statistically significant reduction in the mean number of acid reflux events for subjects in the CJ-040,714 5 mg OD treatment group (p=0.0078) most probably accounted for this observation. There was no evidence to suggest that either dose of CJ-040,714 studied had an effect on any of the other secondary PD parameters.

CJ-040,714 was well tolerated in the study. All AEs were mild or moderate in nature and all events, with the exception of a foot fracture, had resolved before the end of the study. There were no deaths or SAEs. Furthermore, there were no dose reductions and no subjects discontinued from the study. There were no clinically relevant changes in any of the safety parameters.