THE 13TH CONGRESS OF THE
EUROPEAN ASSOCIATION FOR CLINICAL PHARMACOLOGY AND THERAPEUTICS (EACPT)
PRAGUE, CZECH REPUBLIC
JUNE 24-27, 2017

Safety, Tolerability, Pharmacokinetics, and Pharmacodynamics of Escalating Single and Multiple Oral Doses of CJ-12420 (tegoprazan), a Novel Potassium-competitive Acid Blocker (P-CAB) in Healthy Male Subjects

Sungpil Han[1], Hee Youn Choi[1], Yo Han Kim[1], Ji Yeon Nam[2], Geun Seog Song[2], Hyeong-Seok Lim[1], Kyun-Seop Bae[1]

1. Department of Clinical Pharmacology and Therapeutics, College of Medicine, University of Ulsan, Asan Medical Center, Seoul 2. CJ HealthCare Corporation, Seoul, Republic of Korea

Introduction

- Gastroesophageal reflux disease (GERD) is a disorder that the reflux of stomach contents causes troublesome symptoms and complications (Vakil *et al.*).
- CJ-12420 (tegoprazan) is a promising potassium-competitive acid blocker (P-CAB) with therapeutic potential for acid-related diseases, such as GERD (erosive esophagitis, non-erosive reflux disease) and gastric ulcer by reversibly suppressing gastric H^+, K^+-ATPase. Since P-CABs bind to both active and inactive forms of the ATPase pump unlike PPIs, P-CABs have a faster onset of action.
- The aim of this study was to investigate the safety, tolerability, pharmacokinetics and pharmacodynamics of CJ-12420 in healthy volunteers.
(clinicaltrials.gov NCT01473173, refer to the QR code)

Materials and Methods

- A phase I, randomized, double-blind, and placebo-controlled clinical trial was conducted in 56 healthy Korean male subjects.
- In the single ascending dose (SAD) study, 50, 100, 200, and 400 mg QD of CJ-12420 were administered to 32 subjects (CJ-12420 : placebo = 6 : 2 in each dose group, N=8). In the multiple ascending dose (MAD) study, 100 and 200 mg QD of CJ-12420 were administered every 24 hours (CJ-12420 : placebo = 6 : 2 in each dose group, N=8) for 7 days. In the comparative pharmacodynamic study, an active comparator, esomeprazole 40 mg QD, was administered to 8 subjects for 7 days.

Phase I	Cohort 1 SAD	Cohort 2 MAD	Cohort 3 Comparative PD
Number of Subjects Planned	32	16	8
Treatment Period	1 day	7 days	7 days
Investigational Product	CJ-12420 / Placebo (3:1)		Esomeprazole
Dose	50, 100, 200, 400 mg (n = 8 each)	100, 200 mg (n = 8 each)	40 mg (n = 7)

- The plasma concentrations of CJ-12420 and its metabolite, M1 were determined using a validated liquid chromatography-mass spectrometry method. Pharmacokinetics were evaluated by non-compartmental method. A pharmacodynamic biomarker, the continuous measurement of the intragastric pH over 24 hours by nasogastric pH monitoring system was used (Katz *et al.*) and serum gastrin values were measured.
- Safety and tolerability were assessed based on physical examinations, vital signs, clinical laboratory tests, and electrocardiograms.

Results

1. Demographics

A total of 55 subjects who had received at least 1 dose of the study drug were included in the safety analysis (Cohort 1 = 32, Cohort 2 = 16 and Cohort 3 =7). All 55 male subjects participating in the study were Asian. Baseline quantitative physical exam variables were comparable (Table 1).

Table 1. Summary for Age, Weight, Height, and BMI

Trait	Cohort 1 (N=32)	Cohort 2 (N=16)	Cohort 3 (N=7)	Overall (N=55)
Age (years) ± SD	25.13 ± 3.82	26.50 ± 4.29	23.29 ± 3.86	25.29 ± 4.01
Weight (kg) ± SD	72.33 ± 8.20	69.19 ± 7.20	72.04 ± 6.89	71.38 ± 7.76
Height (cm) ± SD	176.97 ± 6.74	173.14 ± 3.84	174.16 ± 3.44	175.50 ± 5.89
BMI (kg/m^2) ± SD	23.10 ± 1.92	23.12 ± 2.04	23.79 ± 1.84	23.19 ± 1.92

2. Pharmacokinetics

In the SAD study, CJ-12420 reached a mean T_{max} at 0.5 to 1.0 hour after dosing and then declined, with a mean elimination half-life ($t_{1/2}$) of 3.65 to 5.39 hours. AUC_{last} (2,519.84 to 24,361.62 ng·h/mL) and C_{max} (669.93 to 5053.22 ng/mL) tended to increase dose-proportionally in SAD study (Figure 1A, Table 2).

In the MAD study, observed ratio of accumulation calculated by AUC ranged from 0.91 to 0.93 after 7 repeated dosing (Figure 1B, Table 3).

Figure 1. Mean plasma concentration time curves of CJ-12420 after (A) single and (B) multiple oral administration.

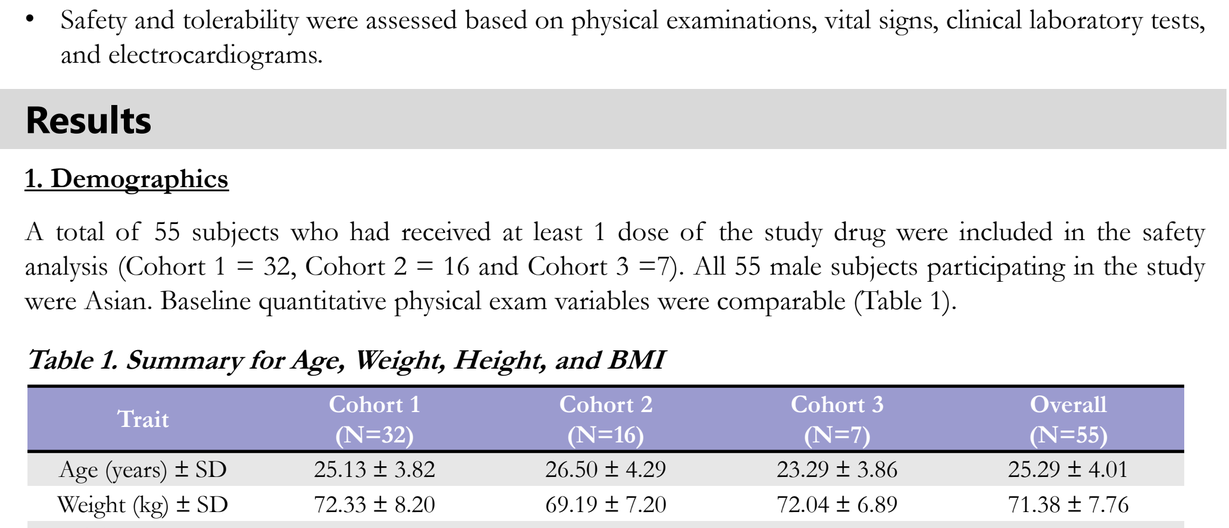


Table 2. Summary of CJ-12420 Plasma PK Parameters Following A Single Oral Doses of 50 mg to 400 mg of CJ-12420 *Extrapolated AUC(%): 100 * (AUC_{inf} – AUC_{last})/AUC_{inf}*

PK Parameters	CJ-12420			
	50mg (N=6)	100mg (N=6)	200mg (N=6)	400mg (N=6)
C_{max} (ng/mL)	669.93 (30.30)	1526.93 (21.64)	2639.20 (33.81)	5053.22 (17.89)
$AUC_{0\text{-last}}$ (ng·hr/mL)	2519.84 (8.73)	6252.23 (25.56)	10030.75 (38.55)	24361.62 (13.18)
$AUC_{0\text{-inf}}$ (ng·hr/mL)	2788.01 (9.41)	6556.17 (23.06)	10478.89 (38.80)	24866.00 (13.45)
t_{max} (hr)	0.5 (0.5-1.5)	1.0 (0.5-1.5)	1.0 (0.5-1.5)	1.0 (1.0-1.5)
$t_{1/2\beta}$	3.65 (0.45)	5.39 (1.11)	4.18 (1.47)	4.63 (0.37)
CL/F (L/hr)	18.00 (1.64)	15.62 (4.03)	20.06 (5.96)	16.21 (2.18)
Vz/F (L)	94.44 (10.10)	117.65 (18.88)	112.30 (29.65)	107.53 (11.30)

C_{max}, $AUC_{0\text{-last}}$ and $AUC_{0\text{-inf}}$ were expressed as geometric mean (geometric CV%). t_{max} was shown as median (min-max). Other PK parameters were shown as arithmetic mean (SD).

Table 3. Summary of CJ-12420 Plasma PK Parameters Following Multiple Oral Doses of 100 mg and 200 mg of CJ-12420

PK Parameters	CJ-12420			
	100 mg (N=6)		200 mg (N=6)	
	Day 1	Day 7	Day 1	Day 7
C_{max} (ng/mL)	1413.33 (24.65)	845.24 (40.70)	2631.54 (35.19)	1241.77 (36.16)
$AUC_{0\text{-24}}$ (ng·hr/mL)	4738.58 (19.88)	4302.86 (23.54)	10204.63 (32.33)	9513.44 (35.27)
t_{max} (hr)	0.76 (0.5-1.0)	1.25 (0.5-4.0)	1.0 (1.0-1.0)	1.75 (1.0-4.0)
$t_{1/2\beta}$ (hr)	3.75 (1.30)	3.69 (1.34)	4.12 (1.35)	7.08 (2.15)
CL/F (L/hr)	21.46 (4.44)	23.80 (6.09)	20.34 (5.47)	21.91 (5.81)
V_z/F (L)	114.17 (35.80)	123.86 (43.51)	114.12 (29.80)	210.08 (37.03)
RAU $AUC_{0\text{-24}}$	-	0.91 (0.10)	-	0.93 (0.07)
RAU C_{max}	-	0.61 (0.15)	-	0.48 (0.11)

$AUC_{0\text{-24}}$, AUC from time 0 to 24 hours after the dose (Day 1 or Day 7); RAU, ratio of accumulation

3. Dose Proportionality

Linear regression analysis was performed to evaluate the relationship between ln(C_{max}), ln(AUC_{last}), and ln(AUC_{inf}) and ln(dose) using a power model, $Ln(Y) = \beta_0 + \beta_1 \cdot Ln(Dose)$ (Table 4, Figure 2).

Figure 2. PK parameter, Ln(C_{max}), Ln(AUC_{last}), and Ln(AUC_{inf}) versus Ln(Dose) of Cohort 1

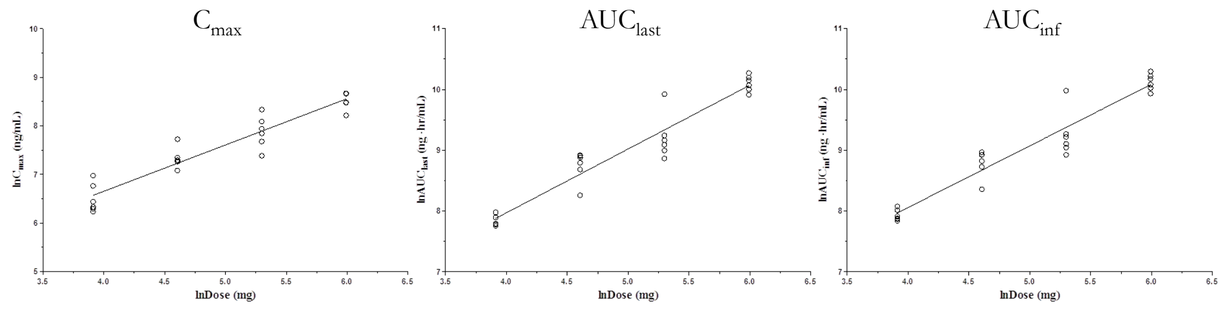


Table 4. Dose Proportionality Assessment of CJ-12420 Plasma Pharmacokinetic Parameters Following A Single Oral Dose

PK Parameters	Slope	p-value	95% Lower Limit	95% Upper Limit
C_{max}	0.953	<.0001	0.813	1.094
$AUC_{0\text{-last}}$	1.050	<.0001	0.915	1.186
$AUC_{0\text{-inf}}$	1.015	<.0001	0.883	1.146

4. Pharmacodynamics

The pharmacodynamic analysis of the SAD and MAD study showed rapid onset and dose-dependent gastric acid suppression. CJ-12420 showed earlier onset of action and less frequent nocturnal acid breakthrough than esomeprazole (Figure 3, 4, 5).

Figure 3. Mean Values of 15-min Median pH Over 24 Hours Following a Single Oral Dose of 50 to 400 mg CJ-12420 (Over 24 – hour period)

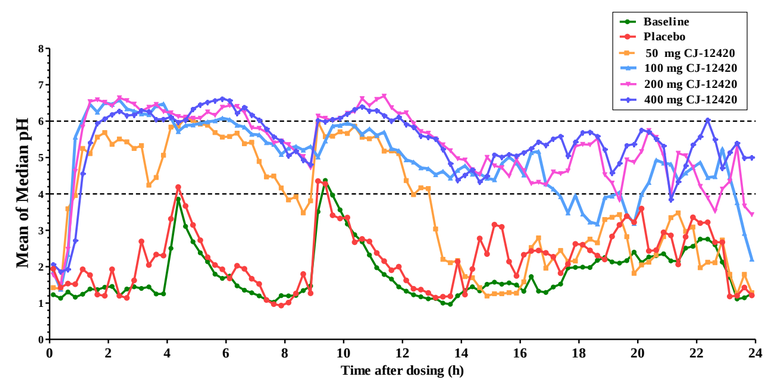


Figure 4 Mean Values of 15-min Median pH Following a Single Oral Dose of 100 mg or 200 mg CJ-12420, or 40 mg Esomeprazole on Day 1 (Over 24-hour period)

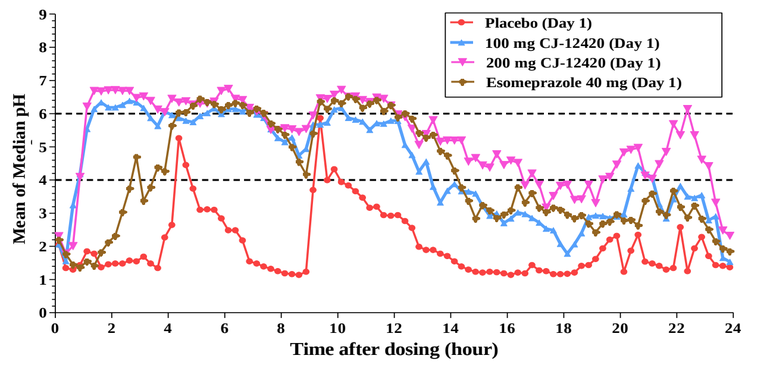
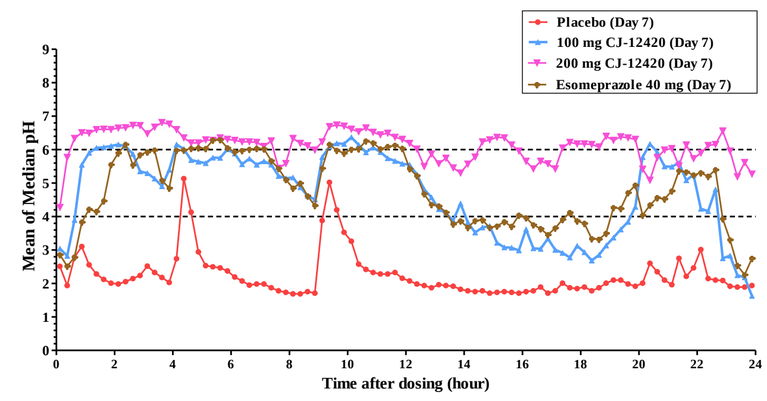


Figure 5 Mean Values of 15-min Median pH Following Multiple Oral Doses of 100 mg or 200 mg CJ-12420, or 40 mg Esomeprazole on Day 7 (Over 24-hour period)



5. Safety and Tolerability

A total of 6 drug related AEs were reported in 6 of 24 subjects treated with CJ-12420 in Cohort 1 (25%) and 4 drug related AEs reported in 4 of 12 subjects treated with CJ-12420 in Cohort 2 (33%). Compared to the Cohort 1 and 2, 4 of 7 subjects treated with 40 mg esomeprazole reported 5 cases of drug related AEs in Cohort 3 (57%). Most of drug related AEs were mild in intensity, except for the one case of moderate headache (Cohort 1) and one case of moderate eye pain (Cohort 3).

All AEs were resolved completely. There were no serious adverse events, and no subject was discontinued due to adverse events. No clinically significant abnormalities in laboratory tests, physical examinations, vital signs, or electrocardiograms occurred.

Conclusions and Discussion

- Oral administration of CJ-12420 in healthy subjects showed linear dose-PK properties among doses tested as well as PD characteristics evaluated by 24 hour gastric pH before and after dosing; the percent of holding time pH > 4 over 24 hours increased in a dose-dependent manner, up to 87% after single dose of CJ-12420 increasing from 50 to 400 mg. After repeated administration of 100 and 200 mg doses of CJ-12420, higher PD parameters (i.e. median pH and percent of holding time pH > 4) were observed, suggesting increased gastric acid suppression.
- Throughout the study, CJ-12420 appeared to be safe and well tolerated up to 400 mg single dose and up to 200 mg repeated doses.
- The tolerable dose ranges and pharmacokinetic and pharmacodynamic characteristics of CJ-12420 evaluated in these studies will be the useful in further clinical development of CJ-12420.

Disclosure

The research hospital, AMC was contracted by the sponsor to design, conduct, analyze, and report this investigation. None of the authors has any intellectual property rights or significant financial interest in CJ-12420, the test product. The authors have indicated that they have no other conflicts of interest.

References

1. Vakil N, van Zanten SV, Kahrilas P, Dent J, Jones R, the Global Consensus Group (2006) The Montreal Definition and Classification of Gastroesophageal Reflux Disease: A Global Evidence-Based Consensus. Am J Gastroenterol 101:1900–1920
2. Katz PO (2006) Review article: intragastric and oesophageal pH monitoring in patients with gastro-oesophageal reflux disease. Aliment Pharmacol Ther 23 Suppl 1:3–11