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GASTRIC ACID SUPPRESSION EFFECT OF TAK-438, A POTASSIUM-COMPETITIVE ACID BLOCKER FOLLOWING ASCENDING MULTIPLE DOSES IN HEALTHY SUBJECTS

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Introduction

TAK-438 is a small molecule, oral potassium-competitive acid blocker under development for the treatment of acid-related disorders. The results of previous phase I studies demonstrated that TAK-438 was well tolerated and at single doses between 20 and 120 mg suppressed gastric acid secretion rapidly, strongly and for a long duration in healthy adult male volunteers.

The objective of these studies was to investigate the safety, tolerability, pharmacokinetics, and pharmacodynamics of multiple rising doses of TAK-438 in healthy male subjects.

Methodology

Two separate studies of similar design were conducted in Japan (JP) and the United Kingdom (UK). Healthy male subjects received multiple rising doses of TAK-438 for 7 days ranging from 10 mg to 40 mg as described Table 1.

Table 1 Study Overview

Region	JP (N=60)	UK (N=48)
Study design	Double blind, placebo controlled, randomized study	Double blind, placebo controlled, randomized study
Subjects	Healthy male Age: 27.4 (years) Body weight: 62.1 (kg)	Healthy male Age: 28.0 (years) Body weight: 75.2 (kg)
Study Drug	Dose escalation: TAK-438 10, 15, 20, 30, 40 mg (N=9/group) Placebo (N=15)	Dose escalation: TAK-438 10, 20, 30, 40 mg (N=9/group) Placebo (N=12)
Endpoint	Safety, PK, and PD	Safety, PK, and PD

24-h intragastric pH monitoring was performed continuously using a calibrated pH monitor. The study was approved by the local Ethics Committee and was conducted under GCP conditions and all applicable local regulations.

Primary variables

Safety: Adverse events, vital signs, ECGs, and laboratory test results
PK: AUC (0-tau), Cmax
PD: Time course of 24h pH, percentage time pH>4 in the 24h period post dose

Results

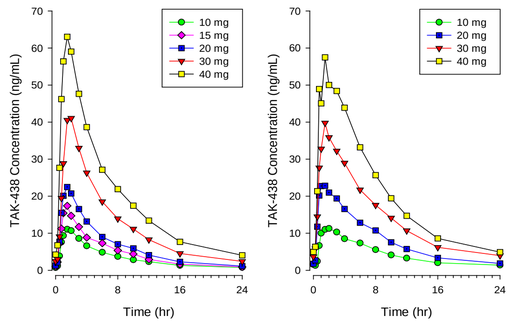

Figure 1 TAK-438 plasma concentration profiles on Day 7 in JP (left panel) and in UK (right panel)

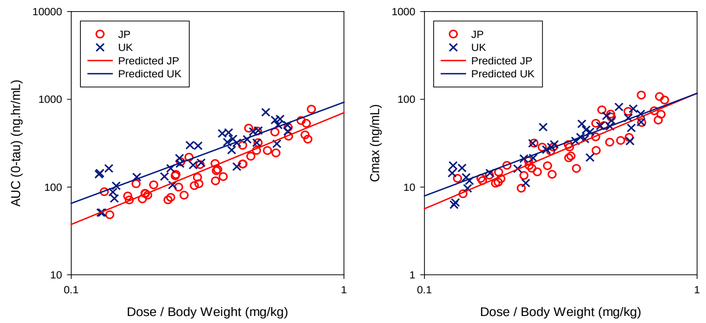

Figure 2 Dose proportionalities of AUC (0-tau) on Day 7 (left panel) and Cmax (right panel) on Day 7 for TAK-438 in JP and UK

Table 2 Evaluation of Dose Proportionality and Ethnic Difference for AUC(0-tau) and Cmax

PK Parameter		Estimate	95% CI Lower	95% CI Upper
AUC(0-tau)	Intercept	6.556	6.336	6.776
	ln (dose/BW)	1.273	1.092	1.455
	region UK	0.275	-0.058	0.609
	region JP	0	.	.
	ln (dose/BW)*region UK	-0.121	-0.383	0.142
	ln (dose/BW)*region JP	0	.	.
Cmax	Intercept	4.765	4.537	4.993
	ln (dose/BW)	1.318	1.129	1.506
	region UK	-0.005	-0.351	0.340
	region JP	0	.	.
	ln (dose/BW)*region UK	-0.149	-0.422	0.123
	ln (dose/BW)*region JP	0	.	.

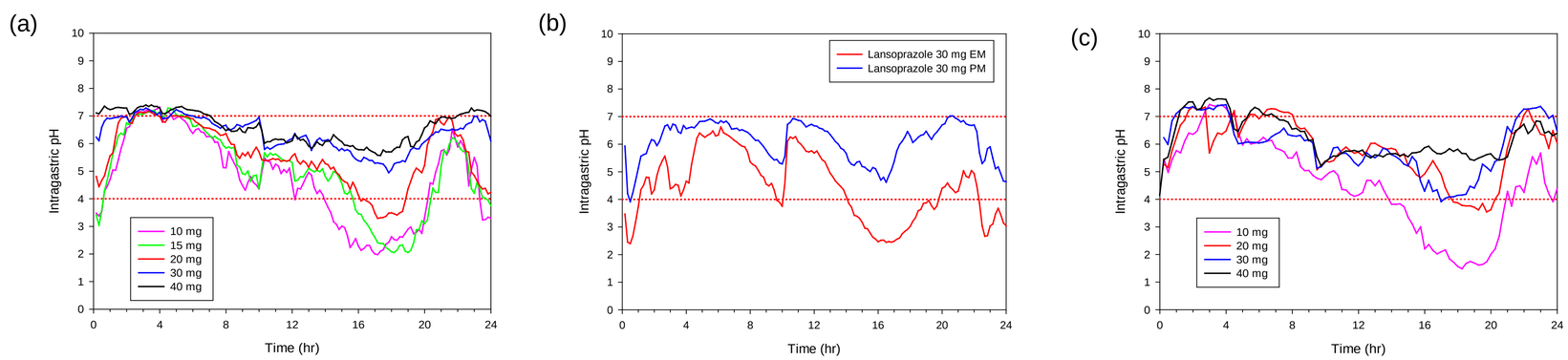

Figure 3 Mean steady-state intragastric pH profiles on Day 7 with multiple administration of TAK-438 in JP (a), Lansoprazole in JP (b), and TAK-438 in UK (c).
EM, extensive metabolizer(CYP2C19 **1/*1*, **1/*2*, or **1/*3*); PM, poor metabolizer (CYP2C19 **2/*2*, **2/*3*, or **3/*3*)
Note: Lansoprazole data in panel (b) is Day 5 data derived from TAK-390MR/CPH-002 study[1] (Not published).

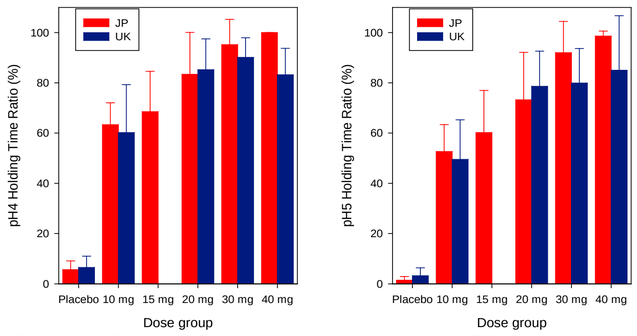

Figure 4 Dose response relationship of pH4HTR (left panel) on Day 7 and pH5HTR on Day 7 (right panel)

Table 3 Treatment-Emergent AEs by Preferred Term in JP study

	Placebo (15)	10 mg (9)	15 mg (9)	20 mg (9)	30 mg (9)	40 mg (9)
Influenza				1		
Nasopharyngitis					1	
Pharyngitis						1
Blood TG increased			1			
Blood UA increased	1					
Eosinophil count increased					1	
Neutrophil count increased	1					
WBC count decreased			1			
Fall			1			

TG: Triglycerides, UA: Uric acid, WBC: White blood cell

Table 4 Treatment-Emergent AEs by Preferred Term in UK study

	Placebo (12)	10 mg (9)	20 mg (9)	30 mg (9)	40 mg (9)
Abdominal pain	1	2			
Toothache				1	
Nasopharyngitis			1		
Oral herpes				1	
Neck pain				1	
Headache	1	1	2		
Oropharyngeal pain	1			1	
Cough	1				
Nasal congestion	1				
Dermatitis contact	1				

Results

Efficacy

- Peak plasma concentrations of TAK-438 occurred by 2 h, declining with an apparent half-life of up to 9 h (Figure 1).
- Plasma exposure for TAK-438 increased with dose, in a slightly greater than dose-proportional manner (Figure 2).
- No statistical difference for AUC(0-tau) and Cmax was observed between JP and UK subjects(Table 2).
- 24-h intragastric pH profiles at different doses show a dose-dependent antisecretory effect.
- Onset of antisecretory effect of TAK-438 appears to be faster when historically compared with Lansoprazole from a separate study (Figure 3).
- A clear dose response relationship was observed in pH4HTR (percentage time pH>4) and pH5HTR (percentage time pH>5) (Figure 4).

Safety

- A total of 9 of 60 subjects (15.0%) experienced 1 or more AEs in the JP study (Table 3).
  A total of 10 of 48 subjects (20.8%) experienced 1 or more AEs in the UK study (Table 4).
- In both studies, increased serum gastrin, pepsinogen I and II levels were observed at all doses studied (data not shown).
- No SAEs were reported in either the JP or the UK study.
- TAK-438 was well tolerated in both studies at multiple doses up to 40 mg.

Summary & Conclusion

Gastric acid secretion was suppressed by TAK-438 rapidly, strongly and for a long duration (including nighttime) following seven days multiple oral doses of up to 40 mg and was well tolerated at all doses studied in healthy subjects.

TAK-438 may therefore offer a safe and well tolerated alternative to PPIs with potential for a greater clinical benefit for the treatment of acid-related disorders.

Reference

1. TAK-390MR/CPH-002 Clinical Study Report, A Phase I, Randomized, Double-Blind, AG-1749 Controlled, Ascending Multiple Dose Study of the Safety, Tolerability, Pharmacokinetics and Pharmacodynamics of TAK-390MR in Healthy Male Subjects

There are no relevant conflicts of interests to disclose.