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GASTRIC ACID SUPPRESSION EFFECT OF TAK-438, A POTASSIUM-COMPETITIVE ACID BLOCKER FOLLOWING ASCENDING SINGLE 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. Faster, higher, and longer increases in gastric pH compared with proton-pump inhibitors (PPIs) may offer a clinical advantage for the treatment of acid-related disorders.

The objective of these studies was to investigate the safety, tolerability, pharmacokinetics and pharmacodynamics of single 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 single rising doses of TAK-438 ranging from 1 mg to 120 mg as described Table 1.

Table 1 Study Overview

Region	JP (N=84)	UK (N=63)
Study design	Double blind, placebo controlled, randomized study	Double blind, placebo controlled, randomized study
Subjects	Healthy male Age: 26.1 (years) Body weight: 62.5 (kg)	Healthy male Age: 26.1 (years) Body weight: 77.7 (kg)
Study Drug	Dose escalation: TAK-438 1, 5, 10, 20, 40, 80, 120 mg (N=9/group) Placebo (N=21)	Dose escalation: TAK-438 1, 5, 10, 15, 20, 30, 40 mg (N=6/group) Placebo (N=21)
	Food Effect: TAK-438 10, 40 mg	Food effect: TAK-438 20 mg
Endpoint	Safety, PK, and PD	Safety, PK, and PD

24-h (JP) / 96-h (UK) 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-inf), Cmax
PD: Time course of 24h pH, percentage time pH>4 in the 24h period post dose

Results

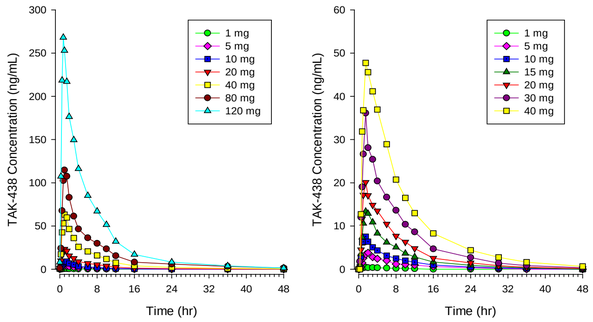

Figure 1 Time course of plasma TAK-438 concentration in JP(left panel) and in UK (right panel)

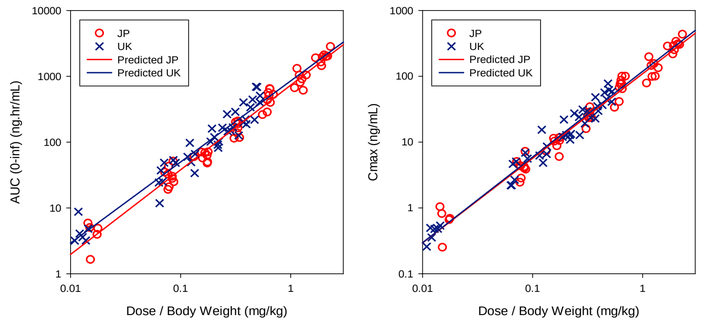

Figure 2 Dose proportionalities of AUC (0-inf) (left panel) and Cmax (right panel) for TAK-438 in JP and UK

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	6.601	6.481	6.721
	ln (dose/BW)	1.286	1.222	1.350
	region UK	0.148	-0.087	0.384
	region JP	0	.	.
	ln (dose/BW)*region UK	-0.054	-0.163	0.056
	ln (dose/BW)*region JP	0	.	.
Cmax	Intercept	4.697	4.588	4.806
	ln (dose/BW)	1.285	1.227	1.344
	region UK	0.083	-0.131	0.296
	region JP	0	.	.
	ln (dose/BW)*region UK	0.017	-0.083	0.116
	ln (dose/BW)*region JP	0	.	.

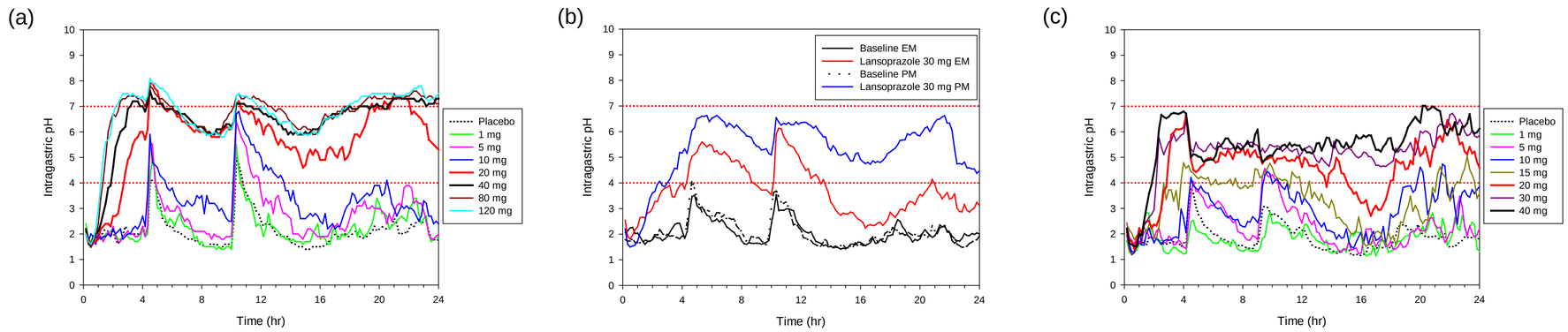

Figure 3 Mean intragastric pH profiles with TAK-438 in JP (a), Lansoprazole in JP (b), and TAK-438 in UK (c).
EM, extensive metabolizer(CYP2C19 **1/*1*, **1/*2*, or **1/*3*); PM, poor metabolizer (CYP2C19 **2/*2*, **2/*3*, or **3/*3*)
Note: Lansoprazole data in panel (b) is Day 1 data derived from TAK-390MR/CPH-002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

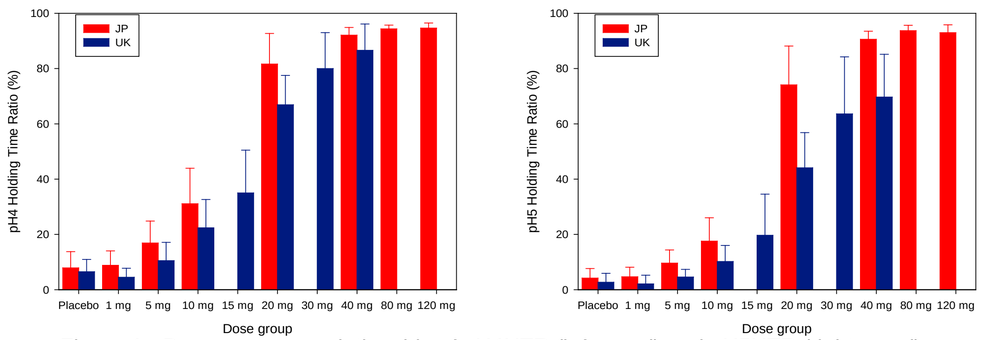

Figure 4 Dose response relationship of pH4HTR (left panel) and pH5HTR (right panel)

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

	Placebo (21)	1 mg (6)	5 mg (6)	10 mg (6)	15 mg (6)	20 mg (6)	30 mg (6)	40 mg (6)
Abdominal pain							1	
Diarrhea							1	
Toothache		1						
Dizziness	1	1						
Headache				1				
Epistaxis					1			
Nasal discomfort	1							
Rhinorrhea	1							
Erythema		1		1				
Dry skin				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.
- No statistical difference for AUC(0-tau) and Cmax was observed between JP and UK subjects (Figure 2 and 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)
- Nighttime values (from 12 to 24 h post dose) for pH >4 and >5, for the 40 mg dose, were 100 and 99% respectively in Japanese subjects. For Caucasian subjects nighttime values (20:00 to 08:00) for pH >4 and >5, for the 40 mg dose, were 90 and 79% respectively (data are not shown).

Safety

- No AEs were reported in the JP study.
- A total of 10 of 63 subjects (15.9%) experienced 12 treatment-emergent AEs in the UK single rising dose study (Cohorts 1 - 7) with no dose-response evident across the cohorts (Table 3).
- No SAEs were reported in either the JP or the UK study.
- In both studies, increased serum gastrin, pepsinogen I and II levels were observed at doses ≥ 10 mg (data not shown).
- TAK-438 was well tolerated in both studies at doses up to 120 mg in JP and 40 mg in the UK.

Summary & Conclusion

Gastric acid secretion was suppressed by TAK-438 rapidly, strongly and for a long duration (including nighttime) at single oral doses between 20 and 120 mg and was well tolerated at all doses studied (1 to 120 mg) 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.