The new P-CAB X482 was safe, tolerable and provided 24h intragastric control, after single oral doses in healthy volunteers

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Erosive GERD (eGERD), a subgroup within the GERD family, is a chronic disorder with prevalence in North America and Europe of more than 10%. Epidemiology data suggest a lower but increasing prevalence in Asia. Available PPIs have a mediocre effect in severe forms of eGERD leaving 20-40% of patients unhealed after 4-8 weeks. A new class of molecules, potassium-competitive acid blockers (P-CABs), represents a different mode of action and the PK profile may allow full acid control both day and night after a single dose. Animal studies of X842, a prodrug of linaprazan, show a slower uptake, lower Cmax and a longer plasma residence time, resulting in a prolonged control of intragastric acidity compared to the main metabolite linaprazan.

The first-in man Phase 1 study of X842 in healthy volunteers comprised a Single Ascending Dose (SAD) part in which four subjects were included in each cohort. The primary objective was to determine the safety and tolerability of X842. The secondary objectives were to determine PK characteristics and PK/PD relationship of X842 and main metabolite. PD was assessed using an intragastric 24h pH-metry and sequential dose levels were tested. All available safety, tolerability, PK and PD data were reviewed prior to proceeding to the next cohort. The initial dose of X842 was 0.08 mg/kg. Standard safety assessments were applied. The Full Analysis Set (FAS) consists of all subjects who had received at least one dose of X842. Results: X842 was safe and well tolerated. No serious or severe adverse events were reported. A clear dose-linearity was observed both for PK and for PD. Full control of 24h intragastric pH was obtained after a single dose of X842. Seventy-two minutes after administration of 2 mg/kg, the intragastric pH value presented as the mean of the 10 minutes median intervals was 4.5. The subsequent pH data showed 100% control of intragastric acidity. All means of the 10 minute median intervals for all four subjects showed pH > 4 throughout the 24 h assessment time.

Conclusion: X842 was safe, well tolerated and provided full 24h intragastric pH control. The results warrant further investigations with X842 in patients with acid-related disorders

X842 mg/kg	C_{max}* ng/ml	$AUC_{0-\infty}$* hxng/ml	$t_{1/2}$* h
0,08	65,58	493,5	5,30
0,2	130,7	948,8	4,98
0,5	213,2	1493	9,15
1,0	518,8	4928	14,4
2,0	955,5	7994	12,1

n=4, *geometric mean, ** in the period 2-24 h after dose (mean)