PHARMACOKINETICS AND PHARMACODYNAMICS OF LINAPRAZAN GLURATE AFTER MULTIPLE ORAL DOSES UP TO 14 DAYS IN HEALTHY SUBJECTS

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Introduction:

Linaprazan glurate (LG), a prodrug to linaprazan, is a next generation P-CAB with excellent clinical efficacy in erosive esophagitis (1).

This study aims to evaluate the pharmacokinetic (PK) and pharmacodynamic (PD) properties of a new formulation of LG which will be used in upcoming phase 3 studies.

Methods:

The acid control properties of LG were presented as the holding time ratio (HTR) and mean pH during Day 1 and 14 of LG administered once daily (QD) or twice daily (BID) at 3 dose levels during 14 days.

Plasma levels of LG and linaprazan were measured to determine pharmacokinetic (PK) parameters, including the area under the plasma concentration-time curve (AUC) and peak plasma concentration (C_{max}).

In total 73 healthy subjects were randomized into six LG dosing groups; 67 subjects completed the study and had at least one evaluable pH measurement (Table 1).

Measurement of intragastric pH was performed during 24 hours on Day 1 and on Day 14, using a pH-measuring electrode in the stomach inserted via nasogastric route. Intragastric pH was measured every second. The pH>4 HTR is presented as the mean of the 10 min median per dose group and day. Blood samplings for PK parameters were also collected.

Results:

Within 2 hours after the first dosing of LG, a mean pH>4 was achieved, in all dose groups but 25 mg QD. The HTRs presented in Table 1 show a dose response with pH>4 and pH>5 HTRs similar at Day 1 and Day 14.

On Day 1, the pH>4 HTR achieves ≈90% in the two highest dosing groups (50 mg and 75 mg BID), and <4% difference observed between these doses at steady state. Additionally, on Day 1 and 14 the pH>5 HTR exceeded 80% in both the 50 mg and 75 mg BID dosing groups.

The HTR for pH>4 and pH>5 were higher with 25 mg BID compared to 50 mg QD, indicating improved pharmacodynamic efficacy with divided dosing.

Without exception, all individual participants maintained a pH>4 for 80–100% of the time on Day 14 in the 50 mg and 75 mg BID groups (Figure 1).

Linaprazan AUC and C_{max} were comparable on Day 1 and Day 14. AUC and C_{max} for LG were approximately 10-fold lower than for linaprazan.

One serious adverse event occurred during the study, a concussion that happened before the first dose of IMP. There were no dose-related increases in adverse events or other findings as assessed by physical examinations, vital signs, ECG, and laboratory parameters.

Conclusion:

The PK and PD properties of LG indicate a strong clinical efficacy potential in patients with acid related disease to be confirmed in a phase 3 program.

A rapid onset of effect was observed in the two highest dosing groups, with sustained maintenance of pH>4 in all subjects and a pH>5 HTR exceeding 80% at steady state.

Repeated oral doses of LG at 25, 50, and 75 mg QD and BID over 14 days were safe and well-tolerated.

Reference:

1) Sharma, P et al. Gastroenterology, Volume 164, Issue 6

Table 1: Descriptive Statistics of Percentage of time within intragastric pH categories- based on 10-minute medians of pH.

Day	Statistics	25 mg LG QD (N=12)	50 mg LG QD (N=12)	75 mg LG QD (N=13)	25 mg LG BID (N=9)	50 mg LG BID (N=11)	75 mg LG BID (N=10)
Day 1 pH >4 HTR	**n**	12	12	12	9	11	9
	Mean (SD)	48.0 (23.23)	64.6 (13.33)	68.1 (23.48)	76.0 (13.52)	87.4 (8.62)	94.5 (4.18)
Day 14 pH >4 HTR	**n**	12	12	11	9	11	8
	Mean (SD)	48.5 (30.62)	63.9 (20.09)	87.2 (11.44)	76.9 (20.13)	95.7 (5.55)	99.0 (1.54)
Day 1 pH >5 HTR	**n**	12	12	12	9	11	9
	Mean (SD)	39.2 (22.70)	50.3 (12.36)	58.1 (26.44)	60.5 (20.54)	81.8 (10.77)	88.8 (7.68)
Day 14 pH >5 HTR	**n**	12	12	11	9	11	9
	Mean (SD)	30.3 (20.28)	39.8 (19.85)	61.4 (21.19)	57.4 (28.01)	81.7 (14.94)	91.9 (9.39)

Figure 1. Percent of subjects with proportion of time with intragastric pH>4 at day 14