DDW 2024

View Abstract

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CURRENT CATEGORY: DDW Late-Breaking Clinical
PRESENTATION TYPE: DDW Late-Breaking Oral
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Abstract

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

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ABSTRACT BODY:

Abstract Body : Background:
Linaprazan glurate (LG) is a 2nd generation P-CAB, a prodrug to linaprazan, with promising clinical efficacy in erosive esophagitis (1). The acid control properties of LG were assessed by the holding time ratio (HTR), i.e., percentage of time with intragastric pH>4, during Day 1 and 14 of LG administered once daily (QD) or twice daily (BID) at 3 dose levels. Pharmacokinetic (PK) profiles for LG and Linaprazan were determined, with PK parameters area under the plasma concentration time profile (AUC) and peak plasma concentration (Cmax) derived.

Methods:
73 healthy subjects were randomized into six dosing groups and received IMP; 67 subjects completed the study and had at least one evaluable pH measurement (Table 1). Intragastric pH was measured during 24 hours on Day 1 and Day 14, using a pH measuring electrode inserted via nasogastric route. Intragastric pH was measured every second. pH>4 HTR is presented as the mean of the 10 min median per dose group and day. Blood sampling for PK parameters was also collected.

Results:
A rapid onset of intragastric acid control was achieved after the first dosing of LG, irrespective of dose level, with a clear dose response as seen in Figure 1. HTRs presented in Table 1 also show a dose response with pH>4 HTR similar at Day 1 and Day 14. Already on Day 1, pH>4 HTR reaches approximately 90% in the two highest dosing groups (50 mg and 75 mg BID) with slight differences in acid control seen in steady state. Linaprazan AUC and Cmax were comparable on Day 1 and Day 14. LG's AUC and Cmax were approximately 10-fold lower than linaprazan's.
A *post-hoc* analysis of pH>4 HTR excluding the initial 90 min after first dosing (pH>4 HTR 1.5-24h) showed close resemblance to the Day 14 pH>4 HTR in all dosing cohorts, suggesting near steady state pH-control already 1.5 hours after first dosing. pH>4 HTR 1.5-24h above 90% was observed not only in the 75 mg BID group but also in the 50 mg BID group. Comparing 50 mg QD and 25 mg BID, a more sustained pH>4 HTR was seen with BID dosing, indicating a better pharmacodynamic yield when dividing the dose. One SAE occurred in the study, a concussion before the first dose of IMP. There was no dose-related increase in AEs or other findings as assessed by physical examinations, vital signs, ECG, and laboratory parameters.

Conclusion:
A rapid onset of pH>4 HTR was seen with LG with a clear dose response. The two highest dosing groups achieved above 90% pH>4 HTR excluding the initial 90 min after first dose. Repeated oral doses of LG 25, 50, and 75 mg QD and BID for 14 days were safe and well tolerated.

Reference:
Linaprazan glurate is highly effective in treating moderate to severe erosive esophagitis: a double-blind, randomized, dose finding study, Sharma, P et al. Gastroenterology, Volume 164, Issue 6, S-203 - S-204

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 1 (1.5-24h) pH >4 HTR	n	12	12	12	9	11	9
	Mean (SD)	51.0 (24.91)	68.9 (14.02)	73.7 (24.78)	80.5 (14.12)	91.5 (8.98)	98.1 (3.10)
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)

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

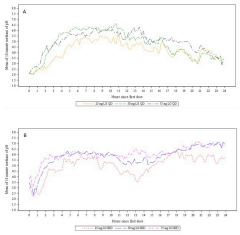

Figure 1: Line plot of mean intragastric pH by treatment in Day 1, A) QD doses, B) BID doses

Disclosure Status

The following authors have completed their 2024 DDW disclosure: Matjaz Flezar: No Answer. | Kajsa Larsson: No Answer. | Kjell Andersson: No Answer. | Gunilla Huledal: No Answer. | Kristofer Katkits: Disclosure completed | Elham Yektaei: Disclosure completed | Peter Unge: No Answer.