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

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Abstract selection

General data

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Abstract body

Introduction: Linaprazan glurate (LG) is a next generation P-CAB, a prodrug to linaprazan, with an excellent clinical efficacy in erosive esophagitis (1-2).
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 and PK parameters, area under the plasma concentration time profile (AUC) and peak plasma concentration (C_{max}) derived.
Aims & Methods: 73 healthy subjects randomized into six dosing groups and received LG, a total of 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, by means of a pH-measuring electrode in the stomach inserted by the 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 samples for PK parameters were also collected.
Results: There was a rapid onset of intragastric acid control achieved already within 90 min after the intake of the first dose of LG, irrespective of dose level, with a clear dose response. The HTRs presented in Table 1 show a dose response with pH>4 HTR similar at Day 1 and Day 14. Already on Day 1, the pH>4 HTR reached approximately 90% in the two highest dosing groups (50 mg and 75 mg BID), with a minor difference in acid control between these doses, particularly at steady state (Table 1).
Linaprazan AUC and C_{max} increased approximately in proportion to dose and were comparable on Day 1 and Day 14. AUC and C_{max} for LG was approximately 10-fold lower than for linaprazan.
A *post-hoc* analysis of the pH>4 HTR excluding the initial 90 min after first dosing (pH>4 HTR 1.5-24h) showed that the pH>4 HTR 1.5-24h was close to the Day 14 pH>4 HTR in all dosing cohorts, suggesting a pH-control near steady state already 1.5 hours after the first dosing. It is noteworthy that a pH>4 HTR 1.5-24h above 90% is seen, not only in the 75 mg BID group as noted in the primary endpoint, but also in the 50 mg BID group (Table 1).
Comparing 50 mg QD and 25 mg BID, a more sustained pH>4 HTR was seen with BID dosing, with more than 10-15 percentage points higher pH>4 HTR already from the start, indicating a better pharmacodynamic yield when dividing the dose.
There was one serious adverse event in the study, a concussion that occurred before the first dose of LG. The most observed treatment emergent adverse event (TEAE) was headache. There was no dose related increase in TEAEs or other findings as assessed by physical examinations, vital signs, ECG, and laboratory parameters.

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 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)

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 the first dose.
Repeated oral doses of LG 25, 50 and 75 mg QD and BID for 14 days were safe and well tolerated.

References

References:

1. LINAPRAZAN GLURATE IS HIGHLY EFFECTIVE IN TREATING MODERATE TO SEVERE EROSIVE ESOPHAGITIS: A DOUBLE-BLIND, RANDOMIZED, DOSE FINDING STUDY. Sharma P *et al,* United European Gastroenterology Journal 2023; 11 (Supplement 8).

1. LINAPRAZAN GLURATE IS WELL TOLERATED IN THE TREATMENT OF PATIENTS WITH EROSIVE ESOPHAGITIS: A DOUBLE-BLIND, RANDOMIZED, DOSE FINDING STUDY, Sharma P *et al*, United European Gastroenterology Journal 2023; 11 (Supplement 8)

Disclosure

Nothing to disclose: No
Disclosure: Kajsa Larsson, Kjell Andersson, Gunilla Huledal, Elham Yektaei and Kristofer Katkits are employees of Cinclus Pharma. Peter Unge is a consultant and senior advisor at Cinclus Pharma.

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