OPTIMISED BIOPHARMACEUTICAL AND PHARMACOKINETIC PROPERTIES OF A LINAPRAZAN GLURATE TABLET FORMULATION TO BE USED IN PHASE 3

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Abstract selection

General data

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Title

Abstract body

Introduction: Linaprazan glurate (LG), a prodrug to linaprazan, is a next generation PCAB with a rapid and extensive effect on gastric pH [1] and up to 93% 4-week healing rate in severe erosive esophagitis in phase 2 study[2].
LG is formulated as tablets, initially with LG as a base. To improve the biopharmaceutical and pharmacokinetic (PK) properties, a new tablet containing LG as HCl salt has been developed. PK of LG HCl tablet was evaluated in two Phase 1 studies.
Aims & Methods: The PK of two tablet formulations were compared in a single-dose, 100 mg LG, 3-way crossover study. Additionally, the food effect on the PK of the LG HCl tablet was assessed. Repeated-dose PK for the LG HCl tablet was evaluated in a randomized, parallel-group study during 14 days of once-daily (25 mg, 50 mg, and 75 mg QD) or twice-daily (25 mg, 50 mg, and 75 mg BID) dosing. Plasma samples were collected to measure LG and linaprazan concentrations and to derive PK parameters.
Results: Healthy subjects were enrolled, with 54 and 72 evaluable for PK analysis in each study, respectively. The exposure to LG was approximately 10 times lower than that of linaprazan following both single and repeated dosing.
The bioavailability of linaprazan from LG HCl salt tablet was approximately 2-fold higher than for LG base tablet as reflected in the geometric LS mean ratio (90% CI) for linaprazan AUC_{inf}: 2.00 (1.83 2.16); C_{max}: 2.32 (2.09-2.57) with a slightly later median t_{max} for the LG HCl tablet (3h vs 2h).
A meal reduced mean AUC_{inf} by 24%, (geometric LS mean ratio (90% CI): 0.76 (0.70-0.82) and mean C_{max} by 55%, (geometric LS mean ratio (90% CI): 0.45 (0.41-0.50), for LG HCl tablet vs fasting intake with a later median t_{max} for linaprazan after fed conditions (6h vs 3h).
Linaprazan C_{max} and AUC increased approximately in proportion to dose, steady state was reached within 5 days, with no accumulation upon 14 days repeated QD or BID dosing of LG HCl tablet. No apparent deviation from time independent PK was seen even if exposure was slightly lower (approximately 20%) than expected for the 75 mg QD and 75 mg BID dosing groups on Day 14.
Mean C_{max} and AUC were slightly lower (10-20%) for the QD vs first BID dose, and slightly lower (15-30%) for the second daily vs the first daily BID dose, most likely due to different conditions with respect to food intake (Table 1).

Table 1: Descriptive Statistics of linaprazan pharmacokinetic parameters

Dose Groups	**C_{max} (nmol/L)** Mean (SD) **Day 1**	**C_{max} (nmol/L)** Mean (SD) **Day 14**	**t_{max} (h)** Median (min-max) **Day 1**	**t_{max} (h)** Median (min-max) **Day 14**	**AUC (nmol/L*h)** Mean (SD) **Day 1**	**AUC (nmol/L*h) 1)** Mean (SD) **Day 14**
25 mg QD	527.25 (184.929)	404.75 (174.068)	5.00 (2.00-14.00)	4.00 (1.25-12.0)	5089 (1607.1)	4640 (1657.4)
50 mg QD	1066.23 (209.973)	1002.00 (538.574)	3.00 (1.00-6.00)	3.03 (1.23-6.00)	9342 (2462.3)	8626 (3571.9)
75 mg QD	1594.42 (585.525)	1044.92 (478.102)	3.50 (1.25-12.00)	3.99 (1.25-13.97)	14 614 (4601.9)	11 697 (4053.3)
25 mg BID Dose 1	658.42 (212.101)	782.92 (263.988)	1.75 (1.25-6.00)	1.50 (1.00-8.03)	4081 (1351.9)	8898 (2247.9)
25 mg BID Dose 2	520.92 (126.378)	520.83 (144.568)	4.00 (2.00-2.47)	4.99 (1.00-6.00)	3947 (939.8)	
50 mg BID Dose 1	1380.18 (303.283)	1148.64 (415.251)	1.50 (1.25-4.00)	1.50 (1.00-4.00)	8084 (1400.5)	13852 (3174.1)
50 mg	997.09	842.36	2.00	4.00	7107	

BID Dose 2	(363.660)	(270.396)	(1.25-11.92)	(1.00-8.00)	(1917.8)	
75 mg BID Dose 1	1942.00 (667.280)	1740.60 (468.197)	1.75 (0.98-6.00)	1.25 (0.85-4.00)	11814 (3181.8)	21366 (4323.8)
75 mg BID Dose 2	1283.90 (435.399)	1285.50 (443.703)	4.00 (1.50-8.08)	1.78 (0.98-8.02)	9532 (2118.1)	

1) AUC Day 1: AUC_{inf} for QD and AUC_{0-12h} and AUC_{12-24h} for BID, AUC Day 14: AUC_{0-24h} for QD and BID

QD: All doses were taken in the evening in a non-fasted state and BID: 1st dose was taken fasted in the morning and the 2nd daily dose in the evening in a non-fasted state.

Conclusion: An optimized linaprazan glurate HCl tablet formulation has been developed for Phase 3, with a later t_{max} and an approximately 2-fold higher bioavailability than the initial tablet and only a minor impact of food intake on linaprazan AUC_{inf}. In addition, the linaprazan glurate HCl tablet provided dose-proportional increase in linaprazan plasma exposure as reflected by AUC and C_{max}.

References

References: 1. Flezar M, et al., UEG Journal, Volume12, Issue S8, Supplement: 32nd United European Gastroenterology Week 2024, October 2024
2. Sharma P, et al. Aliment Pharmacol Ther. 2025 Apr 4. doi: 10.1111/apt.70109. Epub ahead of print. PMID: 40183130.

Disclosure

Nothing to disclose: No

Keywords

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