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

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Introduction: Linaprazan glurate (LG), a prodrug to linaprazan (L), is a next generation P-CAB with a rapid and extensive effect on gastric pH (1) and excellent clinical efficacy in erosive esophagitis (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.

Methods: The PK of the two tablet formulations were compared following a single dose of 100 mg LG in a 3-way cross-over study, and the food effect on the PK of the LG HCl tablet was evaluated. Repeated dose PK was evaluated for the LG HCl tablet following QD (25 mg, 50 mg and 75 mg QD) and BID (25 mg, 50 mg and 75 mg BID) 14-days dosing in a randomized, parallel group study. PK samples were collected to determine LG and L plasma levels and derive PK parameters.

Results: Healthy subjects were dosed with 54 and 72 evaluable for PK in each of the studies.
The exposure of LG was approximately 10-fold lower than for L following single and repeated dosing. The bioavailability of L 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 L AUCinf: 2.00 (1.83 2.16); Cmax: 2.32 (2.09-2.57) with a slightly later median tmax for the LG HCl tablet (3 h vs 2 h) (Figure 1).
A meal reduced mean AUCinf by 24%, (geometric LS mean ratio (90% CI): 0.76 (0.70-0.82) and mean Cmax 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 tmax for L after fed conditions (6 h vs 3 h) (Figure 1).
L Cmax 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 dose groups on Day 14. Mean Cmax and AUC was slightly lower (10-20%) for the QD dose vs first BID dosing, 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).

Conclusion: An optimized linaprazan glurate HCl tablet formulation has been developed for Phase 3, with a later tmax and an approximately 2-fold higher bioavailability than the initial tablet and only a minor effect of food intake on linaprazan AUCinf. In addition, the linaprazan glurate HCl tablet provided dose-proportional increase in linaprazan plasma exposure with respect to AUC and Cmax.

Reference:

1) Fležar M et al. Gastroenterology, Volume 12, Issue 7
2) Sharma, P et al. Gastroenterology, Volume 164, Issue 6

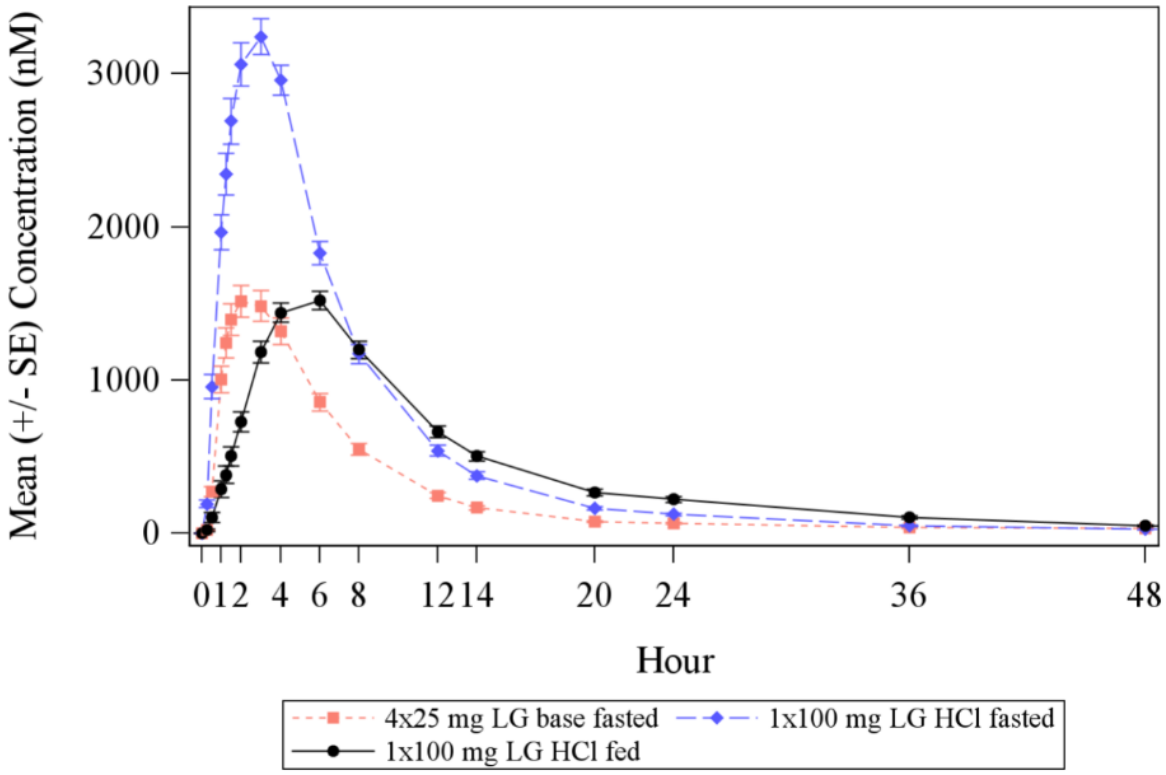

Figure 1. Mean (+/-) linaprazan concentration over time (PK Analysis Set)

Table 1: Descriptive Statistics of linaprazan pharmacokinetic parameters

	C_{max} (nmol/L)		t_{max} (h)		AUC (nmol/L*h) [1)]	
	Mean (SD)		Median (min-max)		Mean (SD)	
	Day 1	**Day 14**	**Day 1**	**Day 14**	**Day 1**	**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)
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)
Dose 2	997.09 (363.660)	842.36 (270.396)	2.00 (1.25-11.92)	4.00 (1.00-8.00)	7107 (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)
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)	

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[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.

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