Pharmacokinetics of Pregabalin Once Daily (QD) Tablet in Healthy Volunteers : Single and Multiple Administration, Dose Proportionality Evaluation Clinical Pharmacology Studies

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Introduction

- Pregabalin QD formulation was developed using **GLARS platform technology** by GL PharmTech Corporation[1), 2)].
- The pharmacokinetic studies were undertaken :

1) to evaluate the **pharmacokinetic properties** of a **single dose** of **pregabalin QD formulation (150mg)** relative to those of twice a day (**BID**) administration of pregabalin IR (**Lyrica Capsule 75mg**) administered after high-fat meal respectively (study 1);
2) to evaluate the **effect of food** on a **single dose** of **pregabalin QD formulation (150mg) administered fasted** relative to those of a **single dose** of **pregabalin QD formulation (150mg) administered after high-fat meal** (study 1) ;
3) to evaluate the pharmacokinetic properties of a **multiple (3 days) dose** of **pregabalin QD formulation (150mg)** administered after evening meal relative to those of twice a day administration of pregabalin IR (**Lyrica Capsule 75mg**) administered after meal during 3 days respectively (study 2);
4) to evaluate the **dose proportionality of four different doses of QD formulation (150, 300, 450 and 600 mg/day, respectively)** administered **after evening meal** in healthy male volunteers (study 3).

Methods

- **Study 1** was a phase I, open-label, randomized, 3-period, 6-sequence crossover study. Healthy male volunteers received **single-dose pregabalin QD formulation** after fasted or after high-fat meal or **twice a day administration of pregabalin IR** after high-fat meal respectively.
- **Study 2** was a phase I, open-label, randomized, 2-period, 2-treatment crossover study. Healthy male volunteers received **single-dose pregabalin QD formulation** after evening meal or **twice a day administration of pregabalin IR** after meal during 3 days respectively.
- **Study 3** was a phase I, open-label, randomized, single dose, parallel study. Each 10 healthy male volunteers randomized for **pregabalin QD formulation of 150, 300, 450 and 600 mg**, respectively. In order to access **dose-proportionality** of pregabalin QD formulation, the **power model** was applied.
- All the study serial blood samples were collected up to 36 hrs for pharmacokinetic evaluation after oral dose. Plasma concentrations of pregabalin were determined by validated LC/MS/MS method. Pharmacokinetic parameters were obtained by noncompartmental methods using Phoenix™ WinNonlin software. Adverse events were monitored throughout all studies.

Results

❖ Study 1 (Single admin. & food effect study)

- Treatment A : Lyrica capsule 75 mg bid (After high-fat meal)
- Treatment B : pregabalin QD formulation 150mg (After high-fat meal)
- Treatment C : pregabalin QD formulation 150mg (Fasted)

Table 1. Comparative pharmacokinetic parameters between pregabalin QD formulation and Lyrica capsule 75mg bid at fed state in healthy male volunteers (N=27)

Pharmaco-kinetic parameters	Geometric LS mean [Tr. A]	Geometric LS mean [Tr. B]	Geometric LS mean [Tr. C]	Point Estimate [B/A]	Point Estimate [B/C]	Confidence Interval [B/A, 90%]	Confidence Interval [B/C, 90%]
C_{max} (ng/mL)	1,624	1,701	1,166	1.047	1.458	[0.971, 1.129]	[1.353, 1.573]
AUC_{last} (hr·ng/mL)	24,110	18.255	11,033	0.757	1.655	[0.694, 0.826]	[1.518, 1.804]
$t_{1/2}$ (hr)	5.71	6.31	7.43	1.105	0.849		
T_{max} (hr)	2.23	4.75	3.03	2.130	1.567		

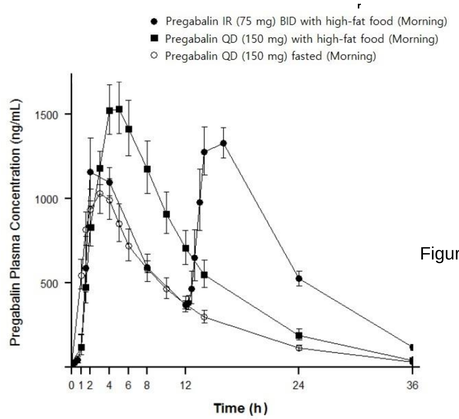

Figure 1. Mean plasma pregabalin concentration-time profiles after single administration of the treatment A, B and C in healthy male volunteers (N=27)

❖ Study 2 (Multiple admin. study)

- Reference : Lyrica capsule 75 mg bid (After standard meal)
- Test : pregabalin QD formulation 150mg (After evening standard meal)

Table 2. Comparative pharmacokinetic parameters after multiple administration during 3 days between pregabalin QD formulation and Lyrica capsule 75mg bid after standard meal in healthy male volunteers (N=24)

Pharmaco-kinetic parameters	Geometric LS mean [Test]	Geometric LS mean [Ref]	Point Estimate [Test/Ref]	Confidence Interval [90%]
$C_{ss,\ max}$ (ng/mL)	2,022	1,583	1.277	[1.210, 1.348]
$C_{ss,\ min}$ (ng/mL)	263	493	0.533	[0.971, 1.129]
$AUC_{T(0\text{-}24)}$ (hr·ng/mL)	23,813	24,444	0.974	[0.933, 1.017]
$t_{1/2}$ (hr)	5.98	5.74	1.042	
T_{max} (hr)	5.88	6.05	0.972	
R	1.07	1.06		

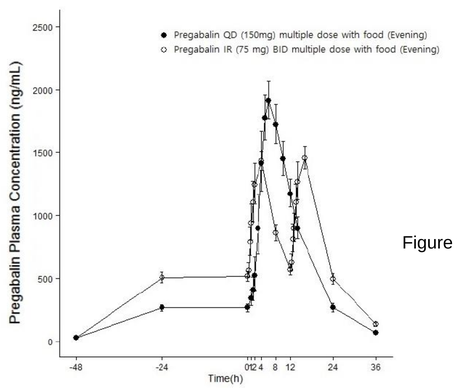

Figure 2. Mean plasma pregabalin concentration-time profiles after multiple administration of pregabalin QD formulation and Lyrica® 75mg capsule bid after standard meal during 3 days (N=24)

❖ Study 3 (Dose-proportionality study)

Table 3. Mean pharmacokinetic parameters along with dose increase of pregabalin QD formulation after evening standard meal in healthy male volunteers

Pharmaco-kinetic parameters	pregabalin QD 150 mg (N=10)	pregabalin QD 300 mg (N=10)	pregabalin QD 450 mg (N=9)	pregabalin QD 600 mg (N=9)
C_{max} (ng/mL)	2,063	3,976	5,800	7,342
AUC_{last} (hr·ng/mL)	26,440	52,996	77,633	106,054
$t_{1/2}$ (hr)	6.51	6.37	6.23	6.23
T_{max} (hr)	6.20	8.20	7.11	7.44
Vd/F (L)	52.24	50.74	50.98	50.10

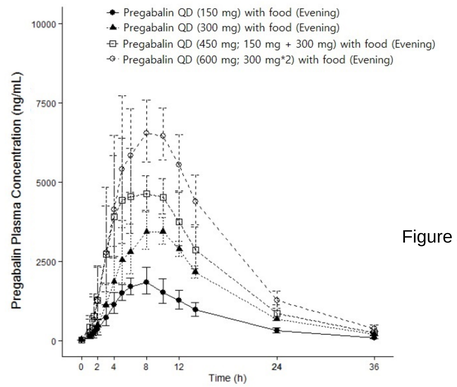

Figure 3. Mean plasma pregabalin concentration-time profiles in various treatments of single administration of ranging from 150mg to 600mg of pregabalin QD formulation in healthy male volunteers

CONCLUSIONS

- There was a dramatic absorption enhancement of pregabalin QD formulation after high-fat morning meal in single administration study, although it was still not sufficient to be comparable to Lyrica® capsule bid in terms of extent of drug absorption (exposure, AUC) despite the equivalence in rate of absorption (peak concentration, C_{max}).
- High-fat food increase pregabalin absorption for pregabalin QD formulation by approximately 65%.
- Study 2 shows a remarkable increase of $AUC_{T(0\text{-}24)}$ of pregabalin QD formulation, getting up for equivalence to Lyrica® capsule bid, which possibly indicate the change of administration time from morning to evening would meet the assumption of further retention followed by additional drug absorption.
- There is a possibility of further drug absorption in pregabalin QD formulation in case of being taken after regular evening meal, which could provide a possible chance of further retention of the tablet in stomach due to posture change in sleeping time, as suggested by Pfizer's research group.
- No serious adverse events and all the adverse events were recovered without any medical action during the treatment as well as after the study; No statistical significance between the treatments.
- Pregabalin QD formulation appeared to be generally well tolerated and to have dose-proportional pharmacokinetics within the clinically recommended dose range in healthy male volunteers.

❖ References

1) J.S. Park, et al. A novel three-layered tablet for extended release with various layer formulations and *in vitro* release profiles. *Drug Development and Industrial Pharmacy*, 2011, 37(6), 664–672.
2) L.A. Hodges, et al. Pharmacoscintigraphy confirms consistent tamsulosin release from a novel triple-layered tablet., *Int. J. Pharm.*, 2013, 454, 41~46.

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