CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

209501Orig1s000

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

Office of Clinical Pharmacology Review

NDA or BLA Number	209501
Link to EDR	\\cdsesub1\evsprod\NDA209501
Submission Date	12/15/2016
Submission Type	*[Standard review]*
Brand Name	Lyrica CR
Generic Name	Pregabalin Extended Release Tablets
Dosage Form and Strength	Extended Release Tablets 82.5, 165, 330 mg
Route of Administration	Oral
Proposed Indication	Management of Neuropathic pain associated with DPN, Management of PHN and Management of Fibromyalgia
Applicant	Pfizer
Associated IND	*[IND107333]*
OCP Review Team	*[Srikanth C. Nallani, Ph.D.]*
OCP Final Signatory	*[Yun Xu, Ph.D.]*

Table of Contents

1. EXECUTIVE SUMMARY

1.1 Recommendations

Review Issue	Recommendations and Comments
Pivotal or supportive evidence of effectiveness	Clinical pharmacology and biopharmaceutics studies supported the dosing regimen used in the clinical trials.
General dosing instructions	Lyrica CR should be administered once daily after an evening meal. Begin dosing of Lyrica CR at 165 mg/day and can be titrated up to 660 mg depending on indication.
Dosing in patient subgroups (intrinsic and extrinsic factors)	Lyrica CR dosing should be adjusted in patients with reduced renal function. Lyrica CR is not recommended in patients with creatinine clearance less than 30 mL/min or who are undergoing hemodialysis.
Labeling	Food-effect and renal function are the two major factors affecting bioavailability of LYRICA CR and these will be described in the label.
Bridge between the to-be-marketed and clinical trial formulations	The to-be-marketed formulation used in clinical trials was also evaluated in the Phase I clinical pharmacology and biopharmaceutics studies.

1.2 Post-Marketing Requirements and Commitments

None.

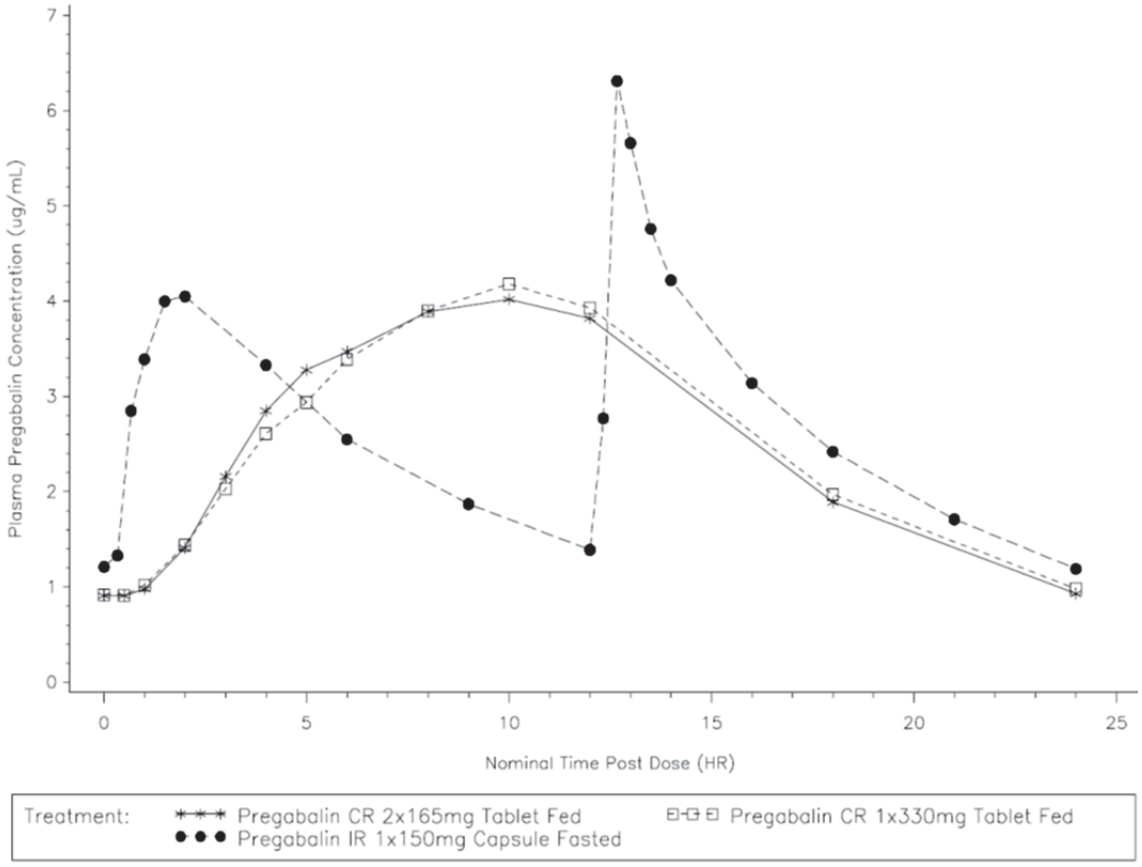
2. SUMMARY OF CLINICAL PHARMACOLOGY ASSESSMENT

2.1 Pharmacology and Clinical Pharmacokinetics

Pregabalin binds with high affinity to the alpha$_2$-delta site (an auxiliary subunit of voltage-gated calcium channels) in central nervous system tissues. Although the mechanism of action of pregabalin has not been fully elucidated, preclinical studies suggest that binding to the alpha$_2$-delta subunit may be involved in pregabalin's anti-nociceptive and antiseizure effects in animals. Lyrica (immediate release capsules of pregabalin also referred to as Lyrica IR or IR in parts of review) is approved as BID or TID dosing for different indications including management of neuropathic pain. Lyrica CR was developed for patient convenience as a once daily formulation to be taken with an evening meal.

LYRICA CR has linear pharmacokinetics with dose-proportional increases in maximum plasma concentration (C_{max}) and area under the plasma concentration-time curve (AUC) from 82.5-660 mg/day (See Appendix 4.2). Following repeated administration, steady-state is achieved within approximately 48-72 hours. LYRICA CR administered once daily following an evening meal has equivalent AUC and lower C_{max} (~40 - 50% lower in single dose studies, ~30 -40% lower in multiple dose studies) relative to a comparative dose of LYRICA administered without food. Variability in C_{max} and AUC for LYRICA CR is less than or equal to 25%. At steady-state, AUC of pregabalin is equivalent but Cmin levels of pregabalin with LYRICA CR are lower by ~20 – 30% compared to LYRICA given twice daily.

Figure: Multiple dose PK of pregabalin after once daily dosing of Lyrica CR taken with food for three days compared to Lyrica IR given twice daily for three days (Study A0081198).



Source: Study Report A0081198 Figure 14.4.2.2.3.

To further compare the pharmacokinetic profile of LYRICA IR and LYRICA CR, partial AUC's in the time intervals of 0-6 hours, 6-12 hours, 12-18 hours and 18-24 hours post dose were calculated and compared. Descriptive statistics of partial AUC (mcg*hr/mL) for pregabalin in different time intervals from study A0081198 are described in Table below for LYRICA CR administered as one 330 mg Tablet Fed or two 165 mg Tablets Fed. Partial AUC of pregabalin was lower in three out of the four post-dose intervals of 6 hours each, as indicated by the ratio of partial AUC expressed as percentage compared to LYRICA IR and the lower 90% CI being below 80 in the 80-125% CI bounds. LYRCIA CR exposure was almost twice as compared to LYRICA IR during the 6-12 hours intervals post-dose (Also see Multiple dose PK in Appendix 4.2).

Similar observation was noted in study A0081216 where LYRICA IR 300 mg BID (600 mg total daily dose for three days) was compared with LYRICA CR (two tablets of 330 mg given once daily with food for three days) (Also see Multiple dose PK in Appendix 4.2).

Table: Descriptive statistics of partial AUC (mcg*hr/mL) for pregabalin in different time intervals from study A0081198.

Parameter	Treatment	N	Mean	SD	Ratio % to IR	Lower 90% CI
AUC0-6	Pregabalin CR 1x330mg Tablet Fed	24	11.95	4.12	54%	42.3
AUC0-6	Pregabalin CR 2x165mg Tablet Fed	23	13.01	3.02	67%	52.5
AUC0-6	Pregabalin IR 1x150mg Capsule Fasted	24	19.08	3.10	Ref	Ref
AUC6-12	Pregabalin CR 1x330mg Tablet Fed	24	22.56	6.50	174%	140
AUC6-12	Pregabalin CR 2x165mg Tablet Fed	23	23.15	4.00	199%	160
AUC6-12	Pregabalin IR 1x150mg Capsule Fasted	24	11.53	1.99	Ref	Ref
AUC12-18	Pregabalin CR 1x330mg Tablet Fed	24	16.85	4.93	70.4%	59.4
AUC12-18	Pregabalin CR 2x165mg Tablet Fed	23	16.89	3.48	75.6%	63.7
AUC12-18	Pregabalin IR 1x150mg Capsule Fasted	24	21.98	3.50	Ref	Ref
AUC18-24	Pregabalin CR 1x330mg Tablet Fed	24	8.52	2.43	77.4%	68.2
AUC18-24	Pregabalin CR 2x165mg Tablet Fed	23	8.54	2.05	79%	70
AUC18-24	Pregabalin IR 1x150mg Capsule Fasted	24	10.54	1.93	Ref	

Data source: Study A0081198. (Also see multiple dose PK in Appendix 4.2, 19 and 20)

Table: Descriptive statistics of partial AUC (mcg*hr/mL) for pregabalin in different time intervals from study A0081216.

Parameter	Treatment	N	Mean	SD	Ratio % to IR	Lower 90% CI
AUC0-6	600 mg Pregabalin IR (300 mg every 12 hours) - Fasted	18	36.54	3.43	Ref	
AUC0-6	660 mg Pregabalin CR (2 X 330 mg) - Fed	18	24.41	3.76	66.3%	61.4
AUC6-12	600 mg Pregabalin IR (300 mg every 12 hours) - Fasted	18	21.67	3.77	Ref	
AUC6-12	660 mg Pregabalin CR (2 X 330 mg) - Fed	18	43.39	5.22	201%	191
AUC12-18	600 mg Pregabalin IR (300 mg every 12 hours) - Fasted	18	42.00	5.89	Ref	
AUC12-18	660 mg Pregabalin CR (2 X 330 mg) - Fed	18	32.48	6.13	76.8%	72.5
AUC18-24	600 mg Pregabalin IR (300 mg every 12 hours) - Fasted	18	21.25	3.58	Ref	
AUC18-24	660 mg Pregabalin CR (2 X 330 mg) - Fed	18	17.47	4.44	81%	76.2

(Also see multiple dose PK in Appendix 4.2, Page 21)

Pregabalin is absorbed from the small intestine and proximal colon. Bioavailability of LYRICA CR is reduced if taken on an empty stomach. The AUC is approximately 30% lower when LYRICA CR is administered fasted relative to following an evening meal. When LYRICA CR is administered following a

600 to 750 calorie (50% carbohydrates, 20% protein, 30% fat) evening meal, peak plasma concentrations occur within approximately 8 to 10 hours and AUC is approximately 93% to 97% relative to a comparative dose of LYRICA. The rate and extent of LYRICA CR absorption is similar when administered following a 400 to 500 calorie, 30% fat or an 800 to 1000 calorie, 15%, 30%, or 50% fat evening meal (See food-effect in section 3.3.3 and Appendix 4.2).

When LYRICA CR is administered following an 800 to 1000 calorie (50% carbohydrates, 20% protein, and 30% fat) morning meal, peak plasma concentrations occur within approximately 12 hours and AUC is 99% relative to a comparative dose of LYRICA. AUC decreases approximately 13% to 25% when LYRICA CR is administered following a 400 to 500 calorie or 600 to 750 calorie (50% carbohydrates, 20% protein, and 30% fat) morning meal relative to the 800 to 1000 calorie meal, while Cmax remains the same (See food-effect in section 3.3.3 and Appendix 4.2).

2.2 Dosing and Therapeutic Individualization

2.2.1 General dosing

Developmental Lyrica CR formulations had lower bioavailability when administered in fasted state compared to fasted Lyrica IR or fed Lyrica CR (Preliminary clinical pharmacology studies using developmental formulation (A00811744 and A0081206)). Therefore the sponsor (b) (4) in final Lyrica CR formulation and administered with food to increase bioavailability (primarily AUC) compared to LYRICA IR.

LYRICA CR should be administered once daily after an evening meal because of the lower bioavailability when taken on an empty stomach. Clinical trials were conducted where patients were advised to take LYRICA CR with an evening meal. LYRICA CR should be swallowed whole and should not be split, crushed, or chewed. When discontinuing LYRICA CR, taper gradually over a minimum of 1 week.

2.2.2 Therapeutic individualization

Conversion from LYRICA capsules or oral solution to LYRICA CR

When switching from LYRICA to LYRICA CR, on the day of the switch, instruct patients to take their morning dose of LYRICA as prescribed and initiate LYRICA CR therapy after an evening meal.

Table: Conversion from LYRICA Capsules or Oral Solution to LYRICA CR

LYRICA Total Daily Dose (dosed 2 or 3 times daily)	LYRICA CR Dose (dosed once a day)
75 mg/daily	82.5 mg/day
150 mg/daily	165 mg/day
225 mg/daily	247.5 mg/day[a]
300 mg/daily	330 mg/day
450 mg/daily	495 mg/day[b]
600 mg/daily	660 mg/day[c]

a. 247.5 mg = 3 × 82.5 mg tablets taken once a day. b. 495 mg = 3 × 165 mg tablets taken once a day.
c. 660 mg = 2 × 330 mg tablets taken once a day.

Patients with Renal Impairment

Pregabalin clearance is nearly proportional to creatinine clearance. In view of dose-dependent adverse reactions and because pregabalin is eliminated primarily by renal excretion, starting dose of LYRICA CR in patients with reduced renal function needs to be reduced. The starting dose in patients with renal impairment is indicated in Table below.

Table: LYRICA CR Dosage Adjustment Based on Renal Function

Creatinine Clearance (CLcr) (mL/min)	Total LYRICA CR Daily Dose (mg/day)				Dose Regimen
Greater than or equal to 60	165	330	495[a]	660[b]	Once a day
30–60	82.5	165	247.5[c]	330	Once a day
Less than or equal to 30/hemodialysis	Dose with LYRICA				

Since the lowest evaluated strength of LYRCIA CR is 82.5 mg, dose adjustment in patients with severe renal impairment or hemodialysis is not possible. Those patients should receive LYRICA (immediate release capsules or solution) instead of LYRICA CR.

2.3 Outstanding Issues

None.

2.4 Summary of Labeling Recommendations

Bioavailability of LYRICA CR is significantly affected by food. The impact of caloric content and fat content on bioavailability of LYRICA CR will be described in the product label.

Pregabalin clearance is nearly proportional to creatinine clearance. Therefore, impact of renal impairment on LYRICA CR PK and dose adjustment will be described in the product label.

3. COMPREHENSIVE CLINICAL PHARMACOLOGY REVIEW

3.1 Overview of the Product and Regulatory Background

Pfizer initiated development of extended-release pregabalin tablet under IND 053763 initially and IND 107333 as a once daily formulation with equivalent total daily doses of Lyrica. However, developmental formulations had lower bioavailability when administered in fasted state compared to fasted Lyrica IR or fed extended-release product (Preliminary clinical pharmacology studies using developmental formulation (A00811744 and A0081206)). Therefore the sponsor (b) (4) in final Lyrica CR formulation and administered with food as an evening meal to increase bioavailability. On August 15, 2008, in an End-of-Phase 2 meeting the sponsor discussed the need for clinical trials with the Agency. The proposal included a series of biopharmaceutics, clinical pharmacology studies and PK/PD analysis based on LYRICA immediate release in lieu of clinical trials. However, Agency indicated on 3/30/2009 "As we noted at the time of our meeting, our standard has been to require at least one adequate and well-controlled efficacy study to confirm that a change in

pharmacokinetic profile does not alter the efficacy when changing from an IR to an ER formulation". Accordingly, the sponsor conducted a clinical trial in patients with pain from Post-herpetic neuralgia (A0081224) and Fibromyalgia (A0081245) using the final formulation. Additionally, the final to-be-marketed Lyrica CR formulation (82.5, 165, and 330 mg) was evaluated in twelve Phase I studies. Lyrica CR has lower exposure when taken under fasting state or when taken in the morning. Therefore, Lyrica CR has to be taken in the evening with a meal.

3.2 General Pharmacology and Pharmacokinetic Characteristics

Relative bioavailability, multiple dose PK, and dose proportionality of 82.5 mg, 165 mg (2x82.5 mg or 1x165 mg), 330 mg (2x165 mg or 1x330 mg), and 660 mg (2x330 mg) pregabalin ER tablets administered once daily following the evening meal relative to 75 mg, 150 mg, 300 mg and 600 mg pregabalin IR capsules administered without food in equally divided doses BID or TID (Studies A0081198, A0081215, A0081216, A0081225, A0081226).

- Lyrica CR (b) (4) needs to be administered with food in the evening compared to Lyrica IR total daily dose. Lyrica CR demonstrates linear and dose-proportional increases in Cmax and AUC of pregabalin. Significant accumulation is not noted and steady-state plasma levels of pregabalin are achieved within 48-72 hours with once daily Lyrica CR administration.

The effect of time of day and food on the PK and relative bioavailability of 330 mg single dose pregabalin ER relative to 300 mg single dose pregabalin IR (Study A0081188, A0081227, A0081228, A0081238, A0081239).

- Food increases bioavailability of Lyrica CR. Across separate studies, higher bioavailability of Lyrica CR was noted when taken with an evening meal compared to morning or mid-day meal.

Clinically significant effect was not observed (<20% decrease in only AUC) with multiple doses of the prokinetic drug erythromycin on the single dose PK of 330 mg pregabalin ER (Study A0081197).

The sponsor did not conduct an in vivo alcohol interaction study because in vitro studies did not show dose-dumping with alcohol containing media. (b) (4) The above were confirmed by biopharmaceutics reviewer Dr. Kelly Kitchens.

Supportive population PK analysis utilizing single dose PK, and multiple dose PK data from healthy and patients (including epilepsy studies) of LYRICA CR along with IR LYRICA was submitted. The key objectives of the population PK analyses were as follows:

- To develop a population PK model to characterize the PK of pregabalin ER in healthy volunteers (EQDD-A008k-DP4-50) and patients with PHN, FM, and partial onset seizures (EQDD-A008k-DP4-96).
- To quantify the variability of key PK parameters (EQDD-A008k-DP4-50, EQDD-A008k-DP4-96).

- To evaluate factors (eg, covariates) that impact pregabalin ER PK (EQDD-A008k-DP4-50, EQDD-A008k-DP4-96).

3.3 Clinical Pharmacology Review Questions

3.3.1 To what extent does the available clinical pharmacology information provide pivotal or supportive evidence of effectiveness?

Clinical pharmacology and biopharmaceutics studies supported the dosing regimen used in the clinical trials. Relative bioavailability described in the review sections 2.2.1, 3.3.3 and Appendix 4.2 helped bridge dosing in general population and dose adjustment in patients with renal impairment.

3.3.2 Is proposed dosing regimen for general population and alternative dosing regimen for subpopulations based on intrinsic factors appropriate?

Relative bioavailability studies conducted comparing LYRICA CR with LYRICA support the proposed dose in general population and dose adjustment with regard to renal function. Pregabalin clearance is nearly proportional to creatinine clearance. In view of dose-dependent adverse reactions and because pregabalin is eliminated primarily by renal excretion, starting dose of LYRICA CR in patients with reduced renal function needs to be reduced. Since the lowest evaluated strength of LYRCIA CR is 82.5 mg, dose adjustment in patients with severe renal impairment or hemodialysis is not possible and hence not recommended with LYRICA CR. Those patients should receive LYRICA (immediate release capsules or solution) instead of LYRICA CR.

Factors	**Dosing Adjustment**	
	Pregabalin IR: Recommendations from USPI	**Pregabalin ER: Proposed Recommendations**
Intrinsic Factors		
Renal Impairment: Normal/Mild (CLcr ≥60 mL/min) Moderate (CLcr 30 to 60 mL/min) Severe (CLcr 15 to 30 mL/min) End stage/hemodialysis (CLcr <15 ml/min)	 150-600 mg/day depending on indication Dose Adjustment Required Dose Adjustment Required Dose Adjustment Required	 165-660 mg/day depending on indication Dose Adjustment Required Not recommended Not recommended
Age	No dose adjustment	No dose adjustment
Sex	No dose adjustment	No dose adjustment
Race	No dose adjustment	No dose adjustment
Hepatic Impairment	No dose adjustment	No dose adjustment
Pregnancy	May cause fetal harm. Advise of potential risk to the fetus.	May cause fetal harm. Advise of potential risk to the fetus.
Breastfeeding	Breastfeeding is not recommended	Breastfeeding is not recommended
Extrinsic Factors		
Food	Can be administered with or without food	Administer following evening meal; if missed, may administer at bedtime following snack or in the morning following snack
Alcohol	Alcohol should be avoided	Alcohol should be avoided
CNS Drugs	Patients may experience additive CNS effects	Patients may experience additive CNS effects
Thiazolidinedione antidiabetic drugs	Physicians to prescribe with caution	Physicians to prescribe with caution
Switching from IR to ER		
On the day of the switch, take pregabalin IR in the morning as prescribed; initiate pregabalin ER after the evening meal.		

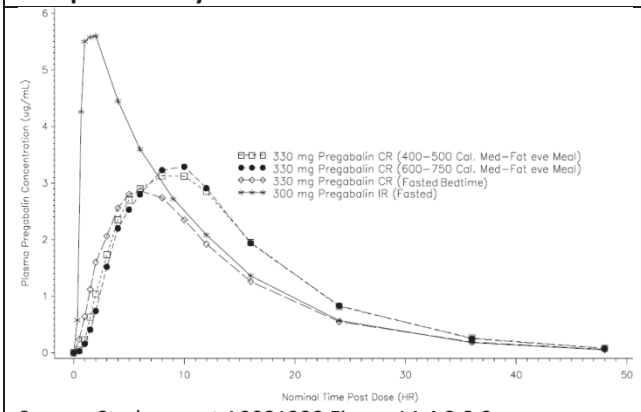
CLcr=creatinine clearance calculated using the Cockcroft-Gault equation.

3.3.3 Are there clinically relevant food-drug or drug-drug interactions and what is the appropriate management strategy?

Drug-Drug Interaction: Pregabalin is absorbed from the small intestine and proximal colon. Effect of rapid gastric emptying was evaluated as a possible drug interaction. Coadministration of multiple doses of gastrointestinal prokinetic, erythromycin (500 mg every 6 h, 3 doses) with a single dose pregabalin ER (330 mg single dose) resulted in a decrease in AUC and Cmax by approximately 17% (90% CI: 77%, 89%) and 13% (90% CI: 82%, 92%), respectively. This observation is not clinically significant and as such dose adjustment is not needed.

Food-effect: LYRICA CR has significant food-effect. Lyrica CR (b) (4) needs to be administered with food in the evening compared to Lyrica IR total daily dose. Study A0081238 investigated the single dose PK of 330 mg commercial image Lyrica CR formulation administered following an evening meal as compared to single dose Lyrica IR capsule formulation administered in the evening fasted. Single-dose administration of 330-mg tablets of the CR formulation (fed: immediately following a 400- to 500-calorie medium-fat evening meal; immediately following a 600- to 750-calorie medium-fat evening meal; and at bedtime approximately 4 hours following completion of a 600- to 750-calorie medium-fat meal) and 300 mg of the IR formulation (fasted) to healthy volunteers (n= 21-24) were generally safe and well tolerated.

Mean Lyrica CR PK profile under fasted or fed compared to Lyrica IR.



Source: Study report A0081238 Figure 14.4.2.2.3

Descriptive Statistics of Plasma Pregabalin PK parameters following Lyrica CR fasted or fed and Lyrica IR fasted.

	Parameter Summary Statistics[a] by Treatment			
Parameter (units)	330 mg CR 400-500 calories Evening Meal	330 mg CR 600-750 calories Evening Meal	330 mg CR Bedtime	300 mg IR Fasted
N^1, N^2	23, 23	24, 24	22, 21	22, 22
AUC_{inf} (µg•h/mL)	54.39 (25)	54.38 (22)	42.20 (32)	61.89 (16)
AUC_{last} (µg•h/mL)	53.52 (25)	53.56 (22)	41.48 (32)	61.20 (16)
C_{max} (µg/mL)	3.373 (19)	3.422 (19)	2.880 (26)	6.414 (21)
T_{max} (h)	8.00 (5.00-12.0)	8.00 (4.00-12.0)	6.00 (3.00-8.02)	1.50 (0.667-6.00)
T_{lag} (h)	0.00 (0.00-5.33)	0.500 (0.00-1.00)	0.00 (0.00-0.500)	0.00 (0.00-0.667)
$t_{½}$ (h)	6.903 (16)	6.889 (16)	7.455 (15)	6.632 (17)

Source: Table 14.4.3.1.
N^1 was the number of subjects in the treatment group; N^2 was the number of subjects included in the analysis.
Parameters are defined in Table 4.
CR = controlled-release; IR = immediate-release; CV = coefficient of variation.
[a] Geometric mean (%CV) was calculated for all parameters except for T_{max} and T_{lag} (median [range]) and $t_{½}$ (arithmetic mean [%CV]).

Source: Study report A0081238 Table 13/Table14.4.3.1.
330 mg CR Bedtime: Administered at bedtime approximately 4 hours following completion of the evening meal.

Cmax of Lyrica CR 330 mg taken with or without food was lower by about half of Lyrica IR 300 mg in fasted state. Ratios of adjusted geometric mean values of Cmax were 52.73%, 53.14%, and 44.93% for the CR treatments with a 400- to 500-calorie evening meal, 600- to 750-calorie evening meal, and at bedtime, respectively, compared to the fasting IR treatment. AUC of Lyrica CR taken with food was statistically bioequivalent to Lyrica IR under fasted state with the 90% CI for ratio of geometric means contained within 80 -125 (see table below); however, Lyrica CR taken fasting at bedtime had 32% lower AUC compared to fasted Lyrica IR.

Table: Statistical summary of treatment comparisons: Lyrica CR under both fed states and fasted taken at bedtime compared to Lyrica IR fasted.

Parameter (units)	Comparison (Test versus Reference)	Adjusted Geometric Means		Ratio (Test/ Ref) of Adjusted Means[a]	90% CI for Ratio
		Test	Reference		
AUC_{inf} (µg•h/mL)	CR 400-500 cal evening meal versus IR	54.78	61.92	88.46	(80.77, 96.89)
	CR 600-750 cal evening meal versus IR	54.38		87.83	(80.21, 96.16)
	CR bedtime versus IR	42.27		68.27	(62.21, 74.92)
AUC_{last} (µg•h/mL)	CR 400-500 cal evening meal versus IR	53.91	61.25	88.01	(80.29, 96.47)
	CR 600-750 cal evening meal versus IR	53.56		87.44	(79.80, 95.81)
	CR bedtime versus IR	41.57		67.87	(61.79, 74.54)
C_{max} (µg/mL)	CR 400-500 cal evening meal versus IR	3.396	6.440	52.73	(48.89, 56.86)
	CR 600-750 cal evening meal versus IR	3.422		53.14	(49.28, 57.29)
	CR bedtime versus IR	2.893		44.93	(41.59, 48.53)

Source: Table 14.4.3.3.1.
Parameters are defined in Table 4.
CR = controlled-release; IR = immediate-release; ref = reference; CI = confidence interval; cal = calorie.
[a] The ratios (and 90% CIs) are expressed as percentages.

Source: Study report A0081238

When compared to Lyrica CR taken fasted, Cmax ratios of fed Lyrica CR treatments met bioequivalent criteria; however, AUC was higher for Lyrica CR under both fed states (See Table below).

Table: Statistical summary of treatment comparisons: Lyrica CR only treatments using bedtime fasted administration as reference.

Parameter (units)	Comparison (Test versus Reference)	Adjusted Geometric Means		Ratio (Test/Ref) of Adjusted Means[a]	90% CI for Ratio
		Test	Reference		
AUC_{inf} (µg•h/mL)	400-500 cal evening meal versus bedtime	54.78	42.27	129.58	(118.13, 142.14)
	600-750 cal evening meal versus bedtime	54.38		128.65	(117.30, 141.09)
AUC_{last} (µg•h/mL)	400-500 cal evening meal versus bedtime	53.91	41.57	129.68	(118.12, 142.36)
	600-750 cal evening meal versus bedtime	53.56		128.84	(117.38, 141.41)
C_{max} (µg/mL)	400-500 cal evening meal versus bedtime	3.396	2.893	117.36	(108.68, 126.73)
	600-750 cal evening meal versus bedtime	3.422		118.27	(109.54, 127.69)

Source: Table 14.4.3.3.2.
Parameters are defined in Table 4.
CR = controlled-release; ref = reference; CI = confidence interval; cal = calorie.
[a] The ratios (and 90% CIs) are expressed as percentages.

Food-Effect (meal composition) on Lyrica CR relative bioavailability at different times of the day:

Several studies were conducted to evaluate the impact of different calorie and fat content on Lyrica CR PK following single dose and multiple dose administration. The bioavailability of Lyrica CR is reduced if taken on an empty stomach. The AUC is approximately 30% lower when Lyrica CR is administered fasted relative to Lyrica CR administered as single dose following an evening meal.

Table: Descriptive statistics of PK Parameters of pregabalin following Lyrica CR administration at different times of day in different single dose PK studies.

Study (A008)	Pregabalin Treatment[a,b]	N, n	AUCinf[c] (µg.h/mL)	Cmax[c] (µg/mL)	Tmax[c] (h)	t½[c] (h)
Evening Administration						
1227	330 mg ER, low-fat, evening	28, 28	60.8 (16)	3.7 (18)	10.0 (5.0–12.0)	6.7 (17)
	330 mg ER, med-fat, evening	28, 27	60.1 (15)	3.6 (18)	10.0 (8.0–16.0)	6.6 (17)
	330 mg ER, high-fat, evening	27, 27	57.6 (16)	3.6 (19)	10.0 (6.0–16.0)	6.5 (18)
	300 mg IR, med-fat, evening	27, 27	59.1 (12)	5.4 (19)	4.0 (2.0–6.0)	6.3 (18)
1228	330 mg ER, med kcal, evening	24, 24	50.8 (21)	3.1 (16)	8.0 (4.0–12.1)	6.7 (14)
	330 mg ER, fasted, evening	23, 23	35.5 (36)	2.6 (25)	5.0 (1.0–12.1)	7.5 (18)
	300 mg IR, fasted, evening	23, 23	58.0 (14)	6.7 (22)	1.5 (0.67–4.0)	6.4 (14)
1238	330 mg ER, low kcal, evening	23, 23	54.4 (25)	3.4 (19)	8.0 (5.0–12.0)	6.9 (16)
	330 mg ER, med kcal, evening	24, 24	54.4 (22)	3.4 (19)	8.0 (4.0–12.0)	6.9 (16)
	330 mg ER, fasted, bedtime[d]	22, 21	42.2 (32)	2.9 (26)	6.0 (3.0–8.0)	7.5(15)
	300 mg IR, fasted, evening	22, 22	61.9 (16)	6.4 (21)	1.5 (0.67–6.0)	6.6 (17)
Morning Administration						
1239	330 mg ER, low kcal, morning	23, 23	40.2 (33)	2.7 (22)	5.0 (4.0–12.0)	7.2 (17)
	330 mg ER, med kcal, morning	23, 23	46.3 (34)	2.7 (23)	8.0 (4.0–12.0)	7.0 (19)
	330 mg ER, high kcal, morning	24, 24	53.4 (22)	2.8 (19)	12.0 (4.0–16.0)	6.7 (17)
	300 mg IR, fasted, morning	23, 23	54.0 (16)	6.3 (24)	1.5 (0.67–2.0)	6.7 (18)
Lunch (Midafternoon) Administration						
1188	330 mg ER, low kcal, mid-day	25, 24	47.5 (28)	2.9 (20)	6.0 (4.0–16.0)	7.0 (16)
	330 mg ER, med kcal, mid-day	26, 24	51.3 (28)	3.2 (26)	6.0 (5.0–10.0)	6.9 (12)
	330 mg ER, high kcal, mid-day	28, 26	51.0 (24)	3.1 (21)	8.0 (4.0–16.0)	7.0 (15)
	300 mg IR, fasted, mid-day	27, 26	54.9 (16)	6.9 (29)	1.5 (0.67–4.0)	6.5 (15)

[a] Accompanying meals were categorized by either calorie or fat content. Low kcal = 400–500 calories/meal, med kcal = 600–750 calories/meal, and high kcal = 800–1000 calories/meal (in each instance with 30% of calories coming from fat). Low-fat = 15% fat content, med-fat = 30% fat content, and high-fat = 50% fat content (in each instance in a meal of 800-1000 calories).

[b] Summary of only the proposed commercial (with possible exception of film coat color and/or debossing) pregabalin ER treatments (Table 2.7.2.1). The drug manufacturing site for pregabalin ER treatments was (b) (4) for Study A0081225 and (b) (4) for all other studies.

[c] Values are expressed as geometric mean (% coefficient of variation) for AUC_{inf} and C_{max}, median (range) for T_{max} and arithmetic mean (% coefficient of variation) for $t_{½}$.

[d] Pregabalin was administered approximately 4 h after the (medium-calorie) evening meal.

Source: Summary of Clinical Pharmacology Table 2.7.2.11.

Across studies, it appears bioavailability (AUC) of Lyrica CR 330 mg is more consistently comparable to Lyrica IR 300 mg after an evening meal compared to morning or mid-day administration with food (See statistical analysis in the table below). As such Cmax of Lyrica CR is lower compared to IR due to the slow release of the total daily dose over 24 hours.

Table: Statistical analysis of PK Parameters of pregabalin following Lyrica CR administration at different times of day in different single dose PK studies.

Study (A008)	Study Design[a]	Pregabalin Dose (mg)		Test/Ref Ratio (90% CIs)	
		Test (dose [mg])	Ref (dose [mg])	AUC	C_{max}
Single Dose Studies					
Morning Administration (Single Dose)					
1239	ER: 400 kcal, med-fat, morning IR: Fasted, morning	1 x 330	1 x 300	74.70 (67.62, 82.53)	43.02 (40.07, 46.18)
	ER: 600 kcal, med-fat morning IR: Fasted, morning	1 x 330	1 x 300	85.79 (77.65, 94.78)	42.97 (40.02, 46.13)
	ER: 800 kcal, med-fat morning IR: Fasted, morning	1 x 330	1 x 300	99.12 (89.75, 109.46)	44.29 (41.27, 47.54)
Lunch (Midafternoon) Administration (Single Dose)					
1188	ER: 400 kcal, med-fat, mid-day IR: Fasted, mid-day	1 x 330	1 x 300	85.98 (80.93, 91.35)	42.27 (39.33, 45.44)
	ER: 600 kcal, med-fat mid-day IR: Fasted, mid-day	1 x 330	1 x 300	92.67 (87.23, 98.44)	45.42 (42.26, 48.82)
	ER: 800 kcal, med-fat mid-day IR: Fasted, mid-day	1 x 330	1 x 300	92.75 (87.38, 98.45)	44.56 (41.50, 47.84)
Evening Administration (Single Dose)					
1227	ER: 800 kcal, low-fat evening IR: 800 kcal, med-fat evening	1 x 330	1 x 300	103.14 (100.08, 106.30)	68.64 (65.91, 71.49)
	ER: 800 kcal, med-fat evening IR: 800 kcal, med-fat evening	1 x 330	1 x 300	101.80 (98.74, 104.96)	66.98 (64.28, 69.79)
	ER: 800 kcal, high-fat evening IR: 800 kcal, med-fat evening	1 x 330	1 x 300	97.33 (94.42, 100.33)	66.17 (63.52, 68.93)
1228	ER: 600 kcal, med-fat evening IR: Fasted, evening	1 x 330	1 x 300	88.27 (80.41, 96.88)	46.75 (42.34, 51.62)
	ER: Fasted, evening IR: Fasted evening	1 x 330	1 x 300	62.15 (56.55, 68.31)	39.03 (35.31, 43.15)
	ER: 600 kcal, med-fat evening (Test) ER: Fasted, evening (Reference)	1 x 330	1 x 330	142.02 (129.39, 155.89)	119.78 (108.49, 133.26)
1238	ER: Fasted, bedtime IR: Fasted, evening	1 x 330	1 x 300	68.27 (62.21, 74.92)	44.93 (41.59, 48.53)
	ER: 400 kcal, med-fat evening IR: Fasted, evening	1 x 330	1 x 300	88.46 (80.77, 96.89)	52.73 (48.89, 56.86)
	ER: 600 kcal, med-fat evening IR: Fasted, evening	1 x 330	1 x 300	87.83 (80.21, 96.16)	53.14 (49.28, 57.29)

Source: Summary of Clinical Pharmacology Table 2.7.2.12.

4. APPENDICES

4.1 Summary of Bioanalytical Method Validation and Performance

In each study and at specific times, blood samples for PK analysis (approximately 4 mL) were collected into tubes containing sodium heparin (lithium heparin for Study A0081309) to provide a minimum of 1.5 mL plasma for PK analysis. Samples were centrifuged at approximately 1700xg for about 10 min at 4oC within 1-hour of collection. The plasma was stored in appropriately labeled screw-capped polypropylene tubes at approximately -20°C. Plasma samples intended for PK analysis of pregabalin were shipped on dry ice to the designated analytical lab.

Plasma samples for the Phase 1 and Phase 3 studies were analyzed at (b) (4). The bioanalytical study report for each study can be found in the individual clinical study reports. Plasma samples were analyzed for pregabalin concentrations using a validated liquid chromatography/tandem mass spectrometry (LC/MS/MS) assay (Pfizer Analytical Method Report: A0089006 for Study A0081309 and A0089002 for all other studies). The calibration range for the pregabalin assay was 0.0250-10.0 mcg/mL and calibration standard responses were linear over this range by using a weighted (1/concentration squared) linear least squares regression. The lower limit of quantification (LLOQ) was 0.025 mcg/mL. Plasma pregabalin concentrations below the LLOQ were reported as <0.0250 mcg/mL. The between-day assay accuracy, expressed as the percent relative error (%RE) and the between-day assay precision, expressed as %CV of the estimated concentrations of QC samples, were less than 9% and 11%, respectively.

Table below summarizes the assay performance for the 11 Phase 1 biopharmaceutics studies.

Clinical Study	Assay Performance	
	%RE[a]	%CV[a]
Pfizer Analytical Method: A0089002, A0089006[b]		
Assay Laboratory: (b) (4)		
A0081188	-2.3 to 3.3	≤4.7
A0081198	-1.2 to 2.0	≤4.9
A0081215	-0.5 to 3.0	≤3.4
A0081216	-0.8 to 7.0	≤4.9
A0081225	-5.2 to 1.7	≤10.2
A0081226	0.9 to 3.5	≤3.6
A0081227	-3.2 to 3.3	≤3.4
A0081228	-8.3 to -1.7	≤3.7
A0081238	-4.9 to -0.7	≤5.6
A0081239	-6.5 to -3.5	≤8.2
A0081309	-0.8 to 1.3	≤5.2

%CV=percent coefficient of variation; %RE=percent relative error.
[a] Statistics (%RE and %CV) based on mean assay performance of low, medium-low, medium-high, high and dilution (if applicable) Quality Control (QC) samples from all analytical batches meeting acceptance criteria.
[b] Only for Study A0081309

Table below summarizes the assay performance for the clinical pharmacology Study A0081197 as well as the 3 Phase 3 studies.

Clinical Study	Assay Performance	
	%RE[a]	%CV[a]
Pfizer Analytical Method: A0089002 **Assay laboratory:** (b) (4)		
A0081197	1.8 to 6.4	≤3.0
A0081194	-1.2 to 3.0	≤3.4
A0081224	-3.6 to 1.2	≤8.1
A0081245	-3.0 to 0.5	≤6.2

%CV=percent coefficient of variation; QC=quality control; %RE=percent relative error.

a. Statistics (%RE and %CV) based on mean assay performance of low, medium-low, medium-high, high and dilution (if applicable) QC samples from all analytical batches meeting acceptance criteria.

After finalization of PK concentration data for Study A0081224, it was determined that some plasma samples assayed for pregabalin were assayed later than the established stability period of 371 days. These samples were identified in the population PK analysis dataset (n = 319) and evaluated further during the Phase 3 population PK analyses (EQDD-A008k-DP4-96). As no systematic bias was identified, all observations were included in the population PK analyses.

4.2 Clinical PK Assessments

Dose-proportionality following multiple dosing of Lyrica CR with food:

Study A0081225 was an open-label, multiple-dose, randomized, 4-period, 4-treatment, cross-over study in 20 healthy adult volunteers. Subjects received total daily oral doses of Lyrica CR 82.5 mg, 165 mg, 330 mg, and 300 mg of the Lyrica IR formulation. The Lyrica CR formulations were administered QD immediately following a standardized medium fat evening meal consisting of 600 to 750 calories with 30 to 35% of the total caloric content coming from fat. The Lyrica IR formulation was administered as 150 mg every 12 hours. The IR doses on the day of PK sampling were administered in the fasted state. All other IR doses were administered irrespective of meal time. For each period, subjects were housed as in-patients from Day 1 through the 24 hour PK assessment on Day 4 (ie, study medication administration began with the evening dose on Day 1). Plasma was collected for PK analysis with serial sampling following the evening dose on Day 3.

Peak pregabalin concentrations following the Day 3 evening dose occurred later for the Lyrica CR tablets (median Tmax 8 hours) than for the IR capsule (median Tmax 1.5 hours). Peak and total exposure (Cmax and AUCτ, respectively) were similar for CR and IR formulations at comparable doses: the observed Cmax for the 330 mg/day CR treatment was similar to that for the 300 mg/day IR treatment (150 mg BID), while the observed AUCτ for the 165 mg CR formulation (τ = 24 hours) was similar to that for the 150 mg IR capsule (τ = 12 hours) (See Table below). Apparent terminal t½ was also similar for all treatments, with arithmetic mean values of 5.6 hours for the IR capsule and 5.7 to 6.0 hours for the 3 CR tablets. Plasma Cmin (the lowest concentration observed at any time during the 12-hour dosing interval for the IR or the 24-hour dosing interval for the CR) was approximately 30% lower for the CR than for the IR treatment. Measures of Cmax-to-Cmin differences (PTR (Peak to trough ratio), PTF (peak to trough fluctuation), and PTS (peak to trough swing)) were all higher for the CR than for the IR, reflecting the lower overall Cmin concentration for the CR.

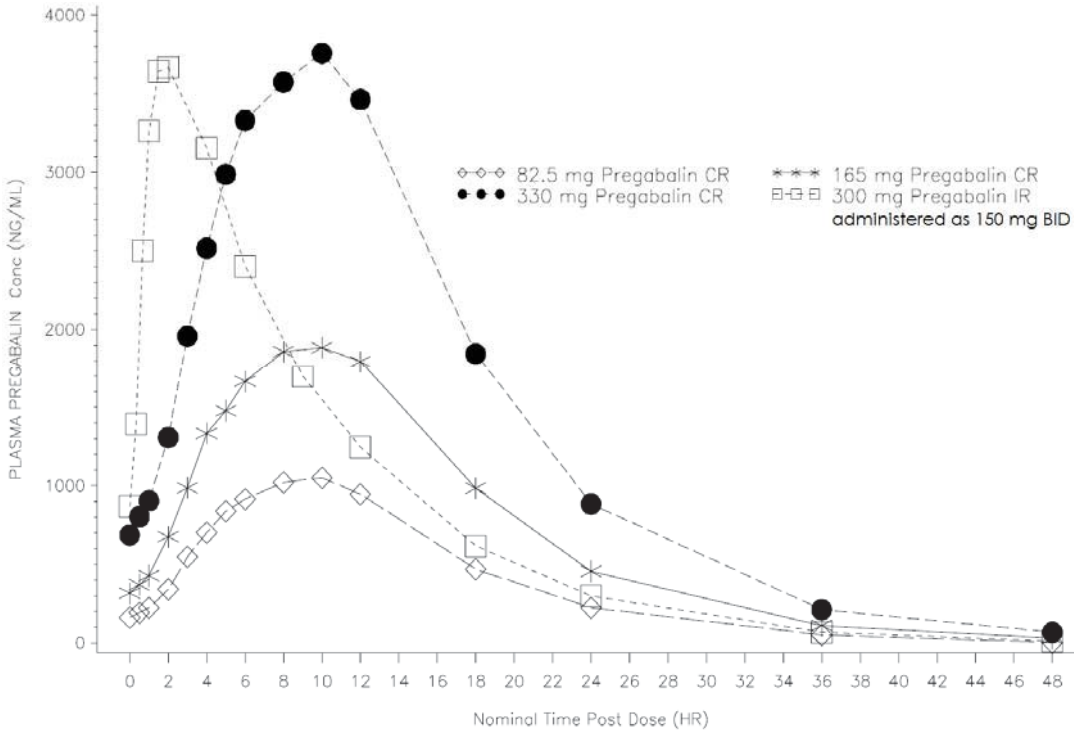
Table: Pregabalin PK parameters following once daily dose of Lyrica CR compared to 150 mg Lyrica IR BID.

	Parameter Summary Statistics[a] by Treatment			
Parameter (units)	82.5 mg/day CR (QD)	165 mg/day CR (QD)	330 mg/day CR (QD)	300 mg/day IR (150 mg BID)
N	20	20	20	20
AUC_τ (µg.hr/mL)	14.95 (21)	28.42 (21)	55.23 (21)	27.90 (18)
C_{max} (µg/mL)	1.117 (17)	2.038 (19)	3.973 (18)	4.085 (20)
T_{max} (hr)	8.00 (5.00-12.0)	8.00 (4.00-12.0)	8.00 (5.00-12.1)	1.51 (0.667-4.00)
$t_{½}$ (hr)	5.725 (17)	5.903 (18)	6.016 (17)	5.647 (18)
C_{min} (µg/mL)	0.1677 (37)	0.3343 (40)	0.6900 (39)	1.016 (28)
C_{av} (µg/mL)	0.6227 (21)	1.184 (21)	2.302 (21)	2.326 (18)
PTR	6.659 (48)	6.096 (51)	5.759 (54)	4.019 (25)
PTF	1.501 (21)	1.414 (23)	1.402 (20)	1.304 (18)
PTS	5.570 (56)	5.008 (60)	4.678 (64)	2.980 (33)

Source: Table 13.5.2. [a] Geometric mean (%CV) for all except: median (range) for T_{max}; arithmetic mean (%CV) for $t_{½}$. M

Source: Study report A0081225 Table 13.5.2.

Figure: Mean plasma pregabalin profiles following Lyrica CR QD and Lyrica IR at Steady-state (Day 3).



Source: Study report A0081225 Figure A10.3.1

Statistical results for the comparison of the CR tablet formulations to the IR capsule are presented in Table below. The parameters were adjusted for dose and regimen prior to the statistical analysis.

Table: Statistical Summary of Treatment Comparisons (Adjusted Parameters): Lyrica CR Formulations Once Daily versus Lyrica IR Formulation Administered Twice Daily.

Parameter, units	Comparison (Test vs Reference)	Adjusted Geometric Means		Ratio (Test/Reference) of Adjusted Means[a]	90% CI for Ratio
		Test	Reference		
AUC_{τ}(adj), µg.hr/mL	82.5 mg CR vs 300 mg IR[b]	29.89	27.90	107.14	103.07, 111.37
	165 mg CR vs 300 mg IR	28.42		101.87	98.00, 105.90
	330 mg CR vs 300 mg IR	27.63		99.03	95.27, 102.94
C_{max}(adj), µg/mL	82.5 mg CR vs 300 mg IR	4.466	4.085	109.32	102.78, 116.27
	165 mg CR vs 300 mg IR	4.075		99.77	93.80, 106.11
	330 mg CR vs 300 mg IR	3.973		97.26	91.44, 103.45
C_{min}(adj), µg/mL	82.5 mg CR vs 300 mg IR	0.6708	1.016	65.99	60.76, 71.68
	165 mg CR vs 300 mg IR	0.6686		65.78	60.56, 71.45
	330 mg CR vs 300 mg IR	0.6900		67.89	62.50, 73.74

Source: Table 13.5.3.1. [a] The ratios (and 90% CIs) are expressed as percentages; [b] The IR capsule treatment (300 mg daily dose) was administered as 150 mg twice daily; CI = confidence interval; CR = controlled release; IR = immediate release; vs = versus.

Source: Study report A0081225. Table 13.5.3.1.

Ratios (test/reference) of the adjusted geometric means for Cmax(adj or dose adjusted) were 109.32%, 99.77%, and 97.26% for the 82.5, 165, and 330 mg CR tablets, respectively, compared to the IR capsule. Corresponding ratios for AUCτ (adj or dose adjusted) were 107.14%, 101.87%, and 99.03% for the 82.5, 165, and 330 mg CR tablets compared to the IR capsule. The 90% CIs surrounding the Cmax (adj) and AUCτ (adj) ratios were within the (80%, 125%) acceptance range for bioequivalence for all 3 CR tablet formulations compared to the IR capsule. Ratios for Cmin (adj) were 65.99%, 65.78%, and 67.89% for the 82.5, 165, and 330 mg CR tablets compared to the IR capsule, indicating approximately 34% lower minimum concentrations for the CR tablets compared to the IR capsule. Note that Cmin is the lowest concentration observed at any time during the 12-hour dosing interval for the IR or the 24-hour dosing interval for the CR. The average concentration (adjusted) across a dosing interval, Cav(ad), was not analyzed statistically. However, the values were similar across all treatments as would be expected given the similar AUCτ (adj) values. Geometric mean Cav(adj) was 2.490, 2.368, and 2.302 mcg/mL over the 24-hour dosing interval for the 82.5, 165, and 300 mg CR treatments, respectively, and 2.326 mcg/mL over the 12-hour dosing interval for the IR treatment.

Multiple-dose PK: Five multiple-dose PK studies were conducted with the overall objective of evaluating PK, relative bioavailability, and dose proportionality of pregabalin ER tablets relative to the comparative dose of pregabalin IR capsules. The PK parameter estimates for the five multiple dose studies are summarized by study in the Table below.

With QD administration following an evening meal, pregabalin ER tablets demonstrated peak plasma concentration approximately 8 to 10 hours post dose. Pregabalin ER demonstrates linear PK with dose proportional increases in AUC, Cmax, and Cmin from 82.5 mg to 660 mg QD. Steady-state, dose-normalized geometric mean Cmax and AUC24 values across studies were similar and ranged from 1.94–2.10 µg/mL/165 mg and 28.9-30.3 µg.hr/mL/165 mg, respectively. Two pregabalin ER tablets administered concurrently QD following the evening meal are bioequivalent to 1 pregabalin ER tablet of the same dose. Similarity in trough (pre-dose C0 and C24) concentrations indicates that steady-state is achieved within 48-72 hours following initiation of pregabalin ER QD dosing. Comparison across studies of the ratio of geometric means for Cmax with QD or single dose pregabalin ER following the evening meal (Cmax, steady-state/ Cmax, single) suggests an accumulation ratio of approximately 1.25. This observation supports the IR to ER conversion proposed.

Table: Descriptive Statistics of Multiple dose PK of LYRICA CR.

Dose[c,d]	Study (A008)	N	Parameters[a,b]						
			AUC (µg.h/mL)	C_{max} (µg/mL)	T_{max} (h)	C_{min} (µg/mL)	Trough C_0 (µg/mL)	Trough C_{24} (µg/mL)	PTF
Preliminary Multiple Dose Study Evaluating the PK and Relative BA of 330 mg Pregabalin ER Administered QD Following an Evening Meal (600-750 Calorie, 30% Fat) Relative to Pregabalin IR Administered q12 without Food									
1 x 330 mg ER q24	1225[d]	20	55.2 (21)	3.97 (18)	8.0 (5.0-12.1)	0.69 (39)	0.86 (39)	0.89 (40)	1.40 (20)
150 mg IR q12	1225[d]	20	27.9 (18)[a]	4.08 (20)	1.51 (0.667-4.0)	1.02 (28)	1.09 (28)	-----[a]	1.30 (18)
Multiple Dose Studies Evaluating the PK, Relative BA, and Dose Proportionality of Proposed Commercial Pregabalin ER Tablets Administered QD Following an Evening Meal (600-750 Calorie, 30% Fat) Relative to Pregabalin IR Administered q12 or TID without Food									
25 mg IR TID	1215	17	15.2 (16)	1.2 (12)	12.7 (1.0-13.0)	0.31 (24)	0.54 (20)	0.57 (20)	1.44 (20)
1 x 82.5 mg ER q24	1215	18	14.7 (18)	1.0 (16)	8.0 (5.0-10.0)	0.20 (30)	0.20 (30)	0.21 (30)	1.33 (17)
75 mg IR q12	1226	24	31.5 (18)	3.2 (21)	12.7 (0.7-13.5)	0.59 (25)	0.62 (25)	0.62 (23)	1.95 (22)
2 × 82.5 mg ER q24	1226	23	30.0 (19)	2.0 (20)	8.0 (4.0-11.9)	0.43 (27)	0.46 (28)	0.47 (30)	1.27 (14)
1 x 165 mg ER q24	1226	24	29.4 (17)	2.0 (17)	8.0 (5.0-11.9)	0.44 (24)	0.47 (25)	0.49 (23)	1.26 (13)
150 mg IR q12	1198	24	62.1 (15)	6.4 (20)	12.7 (0.7-13.5)	1.11 (21)	1.18 (19)	1.15 (24)	2.01 (22)
2 × 165 mg ER q24	1198	22	59.3 (17)	4.1 (16)	10.0 (5.0-12.0)	0.82 (25)	0.88 (25)	0.90 (27)	1.32 (13)
1 x 330 mg ER q24	1198	22	60.1 (18)	4.2 (20)	10.0 (5.0-11.9)	0.85 (26)	0.88 (27)	0.95 (26)	1.33 (15)
300 mg IR q12	1216	18	120.0 (13)	11.4 (17)	12.7 (0.7-14.0)	2.08 (22)	2.13 (22)	2.38 (20)	1.83 (22)
2 × 330 mg ER q24	1216	18	115.5 (14)	7.8 (12)	9.0 (6.0-12.0)	1.76 (26)	1.85 (30)	1.92 (28)	1.24 (11)

BA=bioavailability; C_0=Trough drug concentration at time zero h; C_{24}=Trough drug concentration at time 24 h; N=number of subjects who received treatment and contributed to PK analyses; q12=every 12 h; q24=every 24 h; TID=every 6, 6, and 12 h (eg, 7 AM, 1 PM, 7 PM).

[a] For A0081225, PK parameters were assessed across the 0–12-h interval for pregabalin IR and 0–24-h interval for pregabalin ER. For all other studies, parameters were assessed across the 0–24-h interval for both pregabalin ER and IR. Serial PK sampling started 48 h following the first dose for A0081225 and 72 h following the first dose for the remaining studies.

[b] Geometric mean (%CV) was calculated for all parameters except for C_0 and C_{24} (arithmetic mean [%CV]) and T_{max} (median [range]).

[c] Evening dose pregabalin ER and IR) was administered at 0 h and morning dose (IR) at 12 h and afternoon dose at 18 h (IR for A0081215 only).

[d] Summary of proposed commercial (with possible exception of film coat color and/or debossing) pregabalin ER tablets only (Table 2.7.2.1). The drug manufacturing site for pregabalin ER treatments was (b) (4) for Study A0081225 and (b) (4) for all other studies.

Source: Summary of Clinical Pharmacology Table 2.7.2.10.

Pregabalin ER administered QD following the evening meal demonstrates equivalent AUC24 relative to a comparative dose of pregabalin IR administered BID or TID without food; 90% CI for AUC24 ratio within

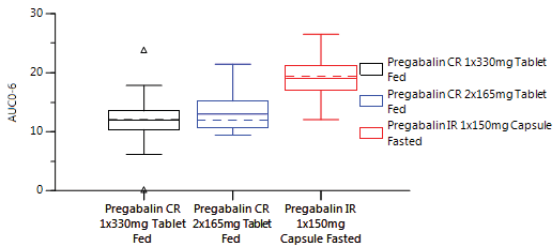
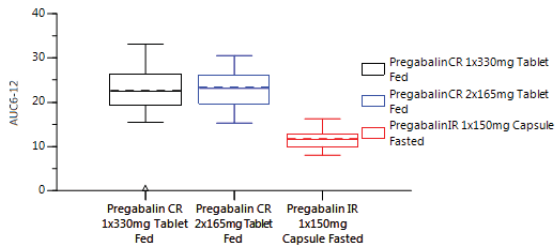
80%-125%). The relative bioavailability of 82.5, 165, 330, and 660 (2 × 330) mg pregabalin ER tablets given QD after a 600-750 calorie medium-fat evening meal is approximately 93% to 97% of pregabalin IR capsules (75, 150, 300, or 600 mg/day). The overall Cmax value (highest concentration observed at any time during the 24-hour period) with pregabalin ER tablets is approximately 63% - 68% or 82% relative to pregabalin IR capsules administered BID or TID, respectively. The overall Cmin value (lowest concentration observed at any time during the 24-hour period) with pregabalin ER tablets is approximately 73% - 84% or 64% relative to pregabalin IR capsules administered BID or TID, respectively (see Table below).

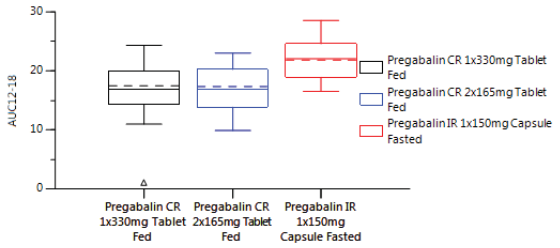
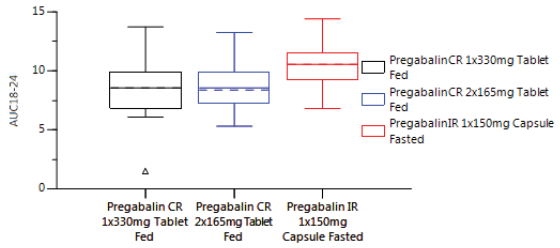
Table: Statistical analysis of multiple dose PK parameters of LYRICA CR.

Study (A008)	Study Design[a]	Pregabalin Dose (mg)		Test/Ref Ratio (90% CIs)[b, c]		
		Test (dose [mg])	Ref (dose [mg])	AUC	C_{max}	C_{min}
Multiple Dose Studies						
Preliminary Multiple Dose Study Evaluating the PK and Relative BA of 330 mg Pregabalin ER Administered QD Following an Evening Meal (600-750 Calorie, 30% Fat) Relative to Pregabalin IR Administered q12 without Food						
1225[a]	ER: 600 kcal, med-fat, evening IR: Fasted, evening	1 x 330 q24	1 x 150 q12	99.03 (95.27, 102.94)	97.26 (91.44, 103.45)	67.89 (62.50, 73.74)
Multiple Dose Studies Evaluating the PK, Relative BA, and Dose Proportionality of Proposed Commercial Pregabalin ER Tablets Administered QD Following an Evening Meal (600-750 Calorie, 30% Fat) Relative to Pregabalin IR Administered q12 or TID without						
1198	ER: 600 kcal, med-fat, evening IR: Fasted, evening	2 x 165 q24	1 x 150 q12	94.56 (92.05, 97.14)	63.84 (60.82, 67.00)	73.32 (69.24, 77.63)
	ER: 600 kcal, med-fat, evening IR: Fasted, evening	1 x 330 q24	1 x 150 q12	97.30 (94.71, 99.95)	66.15 (63.02, 69.42)	78.08 (73.74, 82.67)
1215	ER: 600 kcal, med-fat, evening IR: Fasted, evening	1 x 82.5 q24	1 x 25 TID	96.02 (92.84, 99.30)	82.19 (77.05, 87.67)	63.71 (59.20, 68.56)
1216	ER: 600 kcal, med-fat, evening IR: Fasted, evening	2 x 330 q24	1 x 300 q12	96.29 (92.35, 100.41)	68.34 (63.76, 73.24)	84.44 (74.49, 95.33)
1226	ER: 600 kcal, med-fat, evening IR: Fasted, evening	2 x 82.5 q24	1 x 75 q12	95.21 (92.52, 97.97)	63.79 (61.00, 66.71)	73.32 (69.27, 77.62)
	ER: 600 kcal, med-fat, evening IR: Fasted, evening	1 x 165 q24	1 x 75 q12	93.05 (90.47, 95.71)	62.62 (59.92, 65.43)	74.15 (70.11, 78.41)

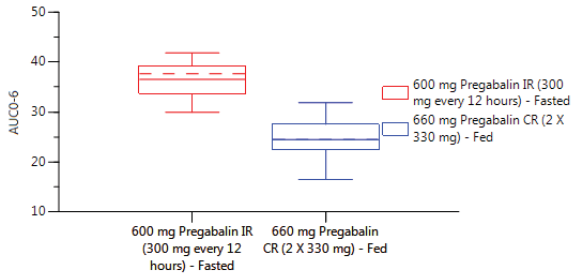
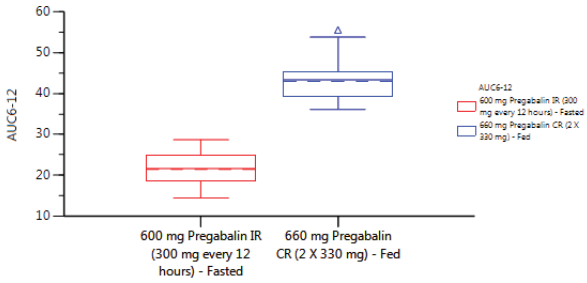
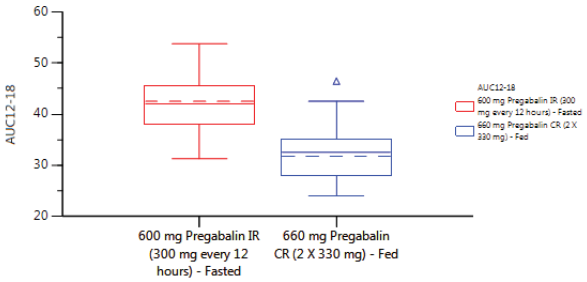
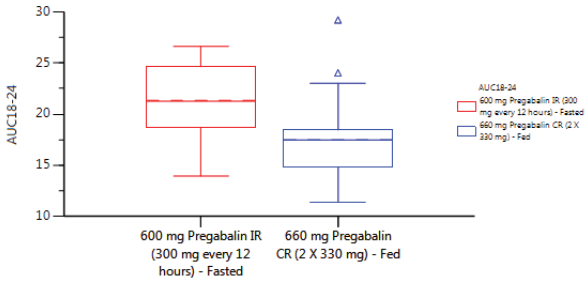
Source: Summary of Clinical Pharmacology Table 2.7.2.12.

Study A0081198 results supplement for summary of clinical pharmacology assessment (Page 4 & 5):

LYRICA IR 150 mg BID Vs LYRICA CR 330 mg QD or LYRICA CR 165 mg two tablets QD pAUC0-6 comparison	LYRICA IR 150 mg BID Vs LYRICA CR 330 mg QD or LYRICA CR 165 mg two tablets QD pAUC6-12 comparison
	
LYRICA IR 150 mg BID Vs LYRICA CR 330 mg QD or	LYRICA IR 150 mg BID Vs LYRICA CR 330 mg QD or

LYRICA CR 165 mg two tablets QD pAUC12-18 comparison	LYRICA CR 165 mg two tablets QD pAUC18-24 comparison
	

Study A0081216 results supplement for summary of clinical pharmacology assessment (Page 4 & 5):

LYRICA IR 300 mg BID Vs LYRICA CR 660 mg QD pAUC0-6 comparison	LYRICA IR 300 mg BID Vs LYRICA CR 660 mg QD pAUC6-12 comparison
	
LYRICA IR 300 mg BID Vs LYRICA CR 660 mg QD pAUC12-18 comparison	**LYRICA IR 300 mg BID Vs LYRICA CR 660 mg QD pAUC18-24 comparison**
	

4.3 Population PK Analyses.

Population Pharmacokinetic Analyses of Pregabalin ER in Healthy Volunteers

A population PK model to describe pregabalin PK in healthy volunteers following administration of pregabalin ER tablets has been developed using serial sampling PK data from 5 Phase 1 studies evaluating pregabalin IR and 9 Phase 1 studies evaluating both pregabalin IR and ER (EQDD-A008k-DP4-50; Section 2.7.2.1.2). A key objective of these analyses was to evaluate covariates that may impact the PK of pregabalin ER. The analysis was performed using nonlinear mixed effects modeling methodology as implemented in the NONMEM software system, version VI or VII (ICON Development Solutions, Ellicott City, MD). The estimation method was first-order conditional estimation method with interaction (FOCEI).

A total of 12,627 plasma concentration samples (6629 with pregabalin ER, 5998 with pregabalin IR) from 335 subjects were included in the analyses. The study population consisted of 230 males and 105 females with ages ranging from 19 to 75 years, and weights ranging from 44.5 to 106.7 kg (Table 7 and Table 8 of report EQDD-A008k-DP4-50). There were 221 White, 73 Black, 2 Asian, and 39 of Other race (Table 7 of report EQDD-A008k-DP4-50). The covariates evaluated in the analysis are listed in Table 2.7.2.13. Covariates were selected for evaluation based on the known PK characteristics of pregabalin and the gastric retentive properties of the pregabalin ER formulation. A full model was established and covariate selection was determined using a stepwise backward elimination procedure with exclusion criteria of objective function value drop of <10.8 ($p<0.001$).

Table: Covariates evaluated in Phase 1 Population PK Model.

Parameter	Covariates
CL	BCCL*, Black race
V	BWT*, age, sex, Black race
Fer	Fed/Fasted*, time of administration (morning, noon, evening, bedtime), sex, Black race, BWT, age, single vs multiple dose
Absorption Parameter-immediate release	Fed/Fasted*, time of administration (morning, evening)*
Absorption Parameter-extended release	Fed/Fasted*, time of administration (morning, noon, evening, bedtime), sex, Black race, BWT, age, single vs multiple dose

BCCL=baseline creatinine clearance; BWT=baseline body weight; CL=pregabalin clearance; F_{er}=bioavailability of pregabalin ER; V=pregabalin volume of distribution.
* Structural covariates included in the base model.
Source: Table 4, EQDD-A008k-DP4-50

A linear one compartment open model with first order elimination was used to characterize the post-absorptive disposition of pregabalin. A first order absorption rate constant and a time varying 3-term absorption model was used to describe the absorption of pregabalin IR capsules given in the fasted and

fed states, respectively. Two separate time varying 3-term absorption models were used to describe the absorption of pregabalin from the ER formulation when administered in the fed or fasted states. Random effects for interindividual variability (IIV) were estimated for CL/V, V, Fer, and KTRE (absorption model parameter associated with underlying rate of absorption for pregabalin ER). Random effects were not estimated for pregabalin IR absorption due to model stability issues.

Table: Parameter Estimates for Phase 1 Population PK model.

	Point Estimate	95% CI[a]
CL (θ_{CL}) [b]	4.66 L/h	4.55–4.77
V	45.1 L	43.6–46.6
$F_{er,fed}$ Pregabalin ER with Food	0.846	0.826–0.866
$F_{er,fasted}$ Pregabalin ER without Food	0.621	0.564–0.678
F_{ir} Pregabalin IR	1	Fixed
Pregabalin ER fed absorption	$0.184\ h^{-1}$	0.172–0.196
KTRE,fed	1.35	1.26–1.44
NTRE,fed	4.71	4.42–5.00
Scale Factor		
Pregabalin ER fasted absorption	$0.177\ h^{-1}$	0.131–0.223
KTRE,fasted	0.564	0.411–0.717
NTRE,fasted	4.71	4.42–5.00
Scale Factor		
Pregabalin IR fasted absorption	$1.13\ h^{-1}$	0.961–1.30
Ka	$1.75\ h^{-1}$	1.20–2.30
Ka, morning	0.169 h	0.168–0.170
T_{lag}		
Pregabalin IR fed absorption	$0.683\ h^{-1}$	0.440–0.926
KTRI,fed	2.46	2.09–2.83
NTRI,fed	2.31	1.96-2.66
Scale Factor		
Inter-individual Variance		
CL/V	16.4%	14.5–18.2
V	15.0%	13.0–16.8
KTRE (Pregabalin ER)	23.7%	19.7–27.0
F_{er}	11.8%	4.80–16.0
Residual variance		
IR Studies (proportional error)[c]	0.118	0.106, 0.132
ER Studies (proportional error)[c]	0.411	0.166, 0.527

KTRE, NTRE, and scale factor are absorption model parameters describing absorption from pregabalin ER in the fed or fasted state. KTRI, NTRI, and scale factor are absorption model parameters describing absorption from pregabalin IR in the fed state.

[a] 95% CI was calculated using the standard error reported in the NONMEM output.

[b] $CL_i = \theta_{CL} \cdot (BCCL_i / BCCL_{ref})$ where $BCCL_i$ is individual's baseline creatinine clearance and $BCCL_{ref}$ is median of study population (112.7 mL/min).

[c] IR studies: 5 Phase 1 studies evaluating IR only; ER studies: 9 Phase 1 studies evaluating both IR and ER.

Source: Table 14, EQDD-A008k-DP4-50

Table: Covariate parameter estimates for the final Phase 1 population PK model.

Parameter	Covariate	Estimate	95%CI[a]
Pregabalin Clearance			
CL[b]	Black race	0.13	0.072 – 0.188
Pregabalin Volume of Distribution			
V[c]	Weight	0.811	0.649 – 0.973
V[c]	Female sex	-0.186	-0.232 – -0.140
V[c]	Age	-0.226	-0.342 - -0.110
V[c]	Black race	0.183	0.111 – 0.255
Pregabalin ER absorption			
KTRE (fed or fasted)[d]	Weight	0.733	0.515 – 0.951
$KTRE_{fasted}$ (fasted only)[d]	Bedtime	-0.307	-0.476 – -0.138

BCCL=baseline creatinine clearance; BWT=baseline body weight; CL=pregabalin clearance; V=pregabalin volume of distribution.

[a] 95% CI was calculated using the standard error reported in the NONMEM output.

[b] $CL_i = \theta_{CL} \cdot (BCCL_i / BCCL_{ref}) \cdot (1 + \theta_{Black,CL} Black_i)$ where $BCCL_i$ is individual's baseline creatinine clearance and $BCCL_{ref}$ is median of study population (112.7 mL/min), $\theta_{Black,CL}$ is the effect of Black race on CL, and $Black_i$ is flag =1 for Black race, else 0.

[c] $V_i = \theta_V \cdot (BWT_i/BWT_{ref})^{\theta BWT,V} \cdot (AGE_i/AGE_{ref})^{\theta AGE,V} \cdot (1 + \theta_{Female,V} SEX_i) \cdot (1 + \theta_{Black,V} Black_i)$ where BWT_i is individual's baseline body weight, BWT_{ref} is the median of study population (76.6 kg), and $\theta_{BWT,V}$ is the power parameter for the relationship BWT_i/BWT_{ref}, AGE_i is individual's baseline age, AGE_{ref} is the median of the study population (38.1 yr), and $\theta_{AGE,V}$ is the power parameter of the relationship AGE_i/AGE_{ref}, $\theta_{Female,V}$ is the effect of female sex on V, SEX_i is flag=1 for females else 0, $\theta_{Black,V}$ is the effect of Black race on V, and $Black_i$ as defined above.

[d] $KTREi = (\theta_{KTREfasted} \cdot ERFT + \theta_{KTREfed} \cdot ERFD) \cdot (1 + \theta_{BED,KTRE} \cdot DBED) \cdot (BWT_i/BWT_{ref})^{\theta BWT,KTRE}$ where ERFT is a flag=1 for fasted state, else 0, ERFD is a flag for fed state, else 0, $\theta_{BED,KTRE}$ is the effect of bedtime administration in the fasted state on KTRE, DBED is flag=1 for fasted bedtime administration, else 0 and BWT_i/BWT_{ref} is as defined above and $\theta_{BWT,KTRE}$ is the power of the relationship of BWT_i/BWT_{ref}

Source: Table 14, EQDD-A008k-DP4-50

The covariates creatinine clearance on CL, body weight on V, fasted administration (in the morning or at all other times) on the rate of pregabalin IR absorption, and fasted administration on both the rate and the extent of pregabalin ER absorption were included in the base model. Six additional covariates included in the final model were Black race on pregabalin CL; Female sex, age, and Black race on pregabalin V; and body weight and fasted bedtime administration on absorption rate constant KTRE (pregabalin ER formulation). Only renal function (eg, creatinine clearance) shows a clinically relevant impact on pregabalin ER AUC and Cmax exposures. Pregabalin CL was directly related to creatinine clearance. The population estimate of pregabalin CL for the typical subject with baseline creatinine clearance (BCCL) of 112.7 mL/min is 4.66 L/h. This observation is in line with the population PK analysis for LYRICA IR.

Population Pharmacokinetic Analyses of Pregabalin ER in Patients

Additional population PK modeling work characterized the PK of pregabalin ER in patients with PHN (Study A0081224), FM (Study A0081245), and partial onset seizures (Study A0081194).

Study (A008-)	Study Design	Doses Evaluated[a]	Tablet Strengths[b]	PK Sampling Schedule
1224	Double-blind, randomized, placebo-controlled, safety and efficacy study of pregabalin ER in the treatment of patients with postherpetic neuralgia *Randomized Withdrawal Design*: 6-week single-blind pregabalin treatment phase (4 weeks dose adjustment, 2 weeks stable dose) followed by a double-blind randomized withdrawal phase for 13 weeks then 1 week double-blind taper	Flexible dosing based on baseline CLcr (n=801): 165-660 mg QD[c] 82.5-330 mg QD[d] Double blind: Pregabalin (208) Placebo (205)	82.5 mg ER 165 mg ER 330 mg ER	A single PK sample collected at Weeks 4, 6, 11, and/or ET
1245	Double-blind, randomized, placebo-controlled, safety and efficacy study of pregabalin ER in the treatment of patients with fibromyalgia *Randomized Withdrawal Design*: 6-week single-blind pregabalin treatment phase (3 weeks dose adjustment, 3 weeks stable dose) followed by double-blind randomized withdrawal phase for 13 weeks then 1 week double-blind taper	Flexible dosing (n=441) : 165-495 mg QD Double blind: Pregabalin (63) Placebo (58)	165 mg ER 330 mg ER	A single PK sample collected at Weeks 3, 6, 11, and/or ET
1194	Double-blind, randomized, placebo-controlled, parallel group study of pregabalin ER as adjunctive therapy in adults with partial onset seizures *Parallel Design*: 2-week dose escalation phase followed by 12-week maintenance phase then 1-week double-blind taper phase	165 mg QD (n=100) 330 mg QD (n=113) Placebo (n=110)	82.5 mg ER (titration phase only); 165 mg ER; 330 mg ER	A single PK sample collected at Weeks 2, 6 and 10

CLcr=creatinine clearance; ET=early termination from the study; QD=once daily.

[a] Study medication was to be taken once daily within 1 hour following the evening meal. Subjects were instructed to take study medication prior to bedtime with food or in the morning with food in the event of missed evening dosing. Doses not taken by the following morning should have been omitted, and the next dose taken as regularly scheduled in the evening.

[b] Pregabalin ER tablets were the proposed commercial formulation with exception of film-coat color and debossing; Section 2.7.1.1, Table 2.7.1.6).

[c] Subjects with baseline CLcr ≥60 mL/min.

[d] Subjects with baseline CLcr >30 to <60 mL/min.

Utilizing the Phase 1 structural and random effects model population PK analysis was conducted on the sparse sample plasma data from Phase 3 studies. Vast majority of the blood samples for PK assessment from the Phase 3 studies were collected >10 hours post-dose. Due to the lack of data on the absorption and volume of distribution, additional covariate investigation was limited to exploring impact on CL. This analysis is not appended as it appears to be confirming the single and multiple-dose PK data.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

SRIKANTH C NALLANI
09/11/2017

YUN XU
09/11/2017