Table 3 Lacosamide Final Population PK Model Parameter Estimate Derived from Trial SP640

Parameters	Estimates	RSE * [%]
Ka [1/hr]	Ka = θ1	not applicable
θ1	4.0 (Fixed)	not applicable
Ke [1/hr]	ke = θ5	not applicable
θ5	0.0449	1.74
V/f [L]	V/f = θ2 + θ3 ×(LBW-50.6) + θ4 × (height-1.70)	not applicable
θ2	43.4	1.36
θ3	0.544	22.4
θ4	29.4	34.7
IIV on Ka [%]	0 (Fixed)	0 (Fixed)
IIV on Ke [%]	13.1	15.5
IIV on V/f [%]	6.25	35.8
Proportional Residual Error [%]	7.76	6.73

Note: * RSE= Relative Standard Error

Figure 6 Goodness-of-fit Plots for Lacosamide Final Population PK Model Derived from Trial SP640

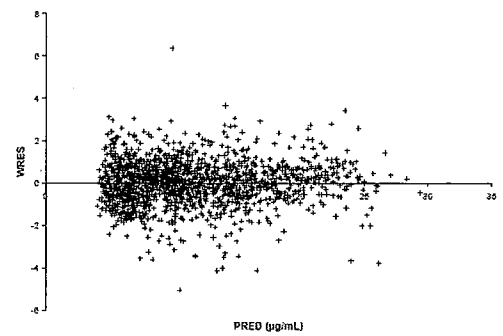
b(4)

Data source: Appendix 6
Dotted line=linear regression (incl. equation and R-squared), line of identity (solid) is included as a reference.

(A)

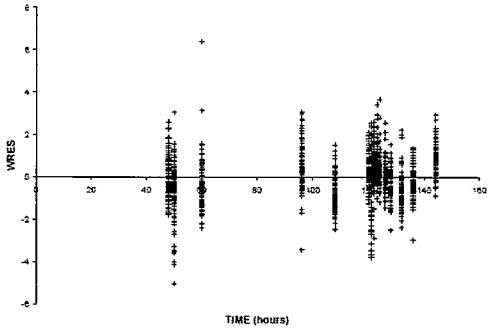
Data source: Appendix 6
Dotted line=linear regression (incl. equation and R-squared), line of identity (solid) is included as a reference.

(B)



Data source: Appendix 6

(C)



Data source: Appendix 6

(D)

Note: (A) is observed versus population predicted
(B) is observed versus individual predicted
(C) is weighted residual versus population predicted
(D) is weighted residual versus time

The population PK dataset was randomly split into two subsets and used for population PK model validation. The validation was preformed by re-analyzing overall dataset and the two subsets using the final model. The results showed that the population PK parameter estimates and the residual variability were comparable for both datasets and comparable with the results form analyzing the complete dataset with all subjects.

5.3.1.1.6 CONCLUSIONS:

- LCM plasma concentrations were adequately described by a 1-compartment model with first order absorption and first-order elimination. Overall, the mean PK parameter estimates for k_e and V/f in healthy subjects of different age and gender were comparable with those determined in other Phase 1 trials (by non-compartmental PK analysis).
- Based on the low IIV of PK parameters of lacosamide (IIV=6.26% for V/f, IIV=13.1% for k_e), it can be concluded that LCM plasma concentrations are highly predictable in the currently evaluated population of healthy subjects. As IIV of LCM plasma concentrations is a priori low, there is not much variability in LCM plasma concentrations that can be explained by possible covariates.
- According to the criteria specified for covariate selection, LBW and height were identified as covariates on V/f among the tested covariates (age, sex, body weight, height, BMI, LBW, CL_{cr}, AP, GGT, AST, ALT, total bilirubin). No parameter was identified as covariate on k_e.
- LBW and height as covariates on V/f reduced the IIV of V/f from 16.8% to 6.3%. The identification of LBW and height as covariates on V/f indicates that the most accurate prediction of V/f of subjects can be done based on LBW (and not based on body weight or other tested covariates) and height of the subjects. A greater LBW or height results in a higher V/f which implicates lower LCM plasma concentrations.
- The observed differences in the pharmacokinetics of LCM in trial SP640 are based on differences in LBW and height. The evaluated model did not identify

sex as a covariate. The impact of sex on the pharmacokinetics of LCM is integrated by inclusion of LBW and height, as male subjects show lager values for mean LBW and mean height compared to females.

- The pharmacokinetics of LCM after multiple administration of high dosages does not change compared to the dosages administered in other Phase 1 trials (eg. SP620).
- A very good prediction of individual LCM plasma concentration profiles is possible using the population PK model evaluated in the current analysis. The only parameters necessary for the individual prediction are LBW and height.

3.2.1.2 Population Pharmacokinetics of Lacosamide in Healthy Subjects with Different Age and Gender, Trial Number: SP- 620

5.3.1.2.1 OBJECTIVES:
The objectives of this population PK analysis were:

1. Characterization of the population pharmacokinetics of LCM in young healthy male and elderly healthy male and female subjects, i.e., the estimation of population PK parameters for volume of distribution (V/f), rate constant of absorption (k_a) and rate constant of elimination (k_e). These population PK parameter estimates characterize the pharmacokinetic (PK) behavior of LCM within the population of healthy subjects in SP620.
2. Identification of important sources of inter-individual variability (relevant demographic or pathophysiologic subject-specific factors, 'covariates') of the PK parameters V/f, k_e and k_a within the trial population.
3. Estimation of the magnitude of residual variability that cannot be described by the population PK model in these subjects.

Based on these results, important information about the differences in the pharmacokinetics of LCM in young healthy male subjects compared to elderly male and female subjects should be gained.

5.3.1.2.2 CLINICAL STUDY OVERVIEW:
The population PK analysis was based on the PK observations from trial SP620.

SP620 was a Phase 1, single-center, double-blind, placebo-controlled, parallel group trial to investigate the pharmacokinetics of unchanged LCM and its metabolite SPM 12809 in plasma and urine in healthy elderly male and female subjects in comparison to young healthy male subjects and to evaluate gender difference in the pharmacokinetics.
12 subjects of each age and gender group were randomized to receive single doses of 100mg lacosamide on Days 1 and 8 and 100mg lacosamide twice daily on Days 4 to 7. In total, 36 subjects were treated with lacosamide and 14 subjects received placebo in SP620. Out of the 36 subjects, 35 completed the trial as planned. Plasma samples were taken at the following time points: 0 (pre-dose), 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 24, 36, 48, 72, 96, 120, 132, 144, and 156 hours following the first dose, pre-dose on Day 8 and 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 24, 36, 48 and 72 hours following the last dose on morning of Day 8. The sponsor performed non-compartmental analysis to obtain pharmacokinetic parameters. In the mean time, they performed population PK analysis by using the same PK data.

5.3.1.2.3 DATA FOR ANALYSIS:
Analysis of plasma samples was performed with a validated high performance liquid chromatography (HPLC) electrospray tandem mass spectrometry (MS/MS) method with the lower limit of quantification (LOQ) of 0.1 µg/mL. All plasma concentrations were

included for the population PK analysis. In total, 1169 records from 36 subjects were included (with a median of 33 samples per subject).

The following parameters were used in the evaluation of possible covariates: Age, Sex (Sex=0 for males, Sex=1 for females), Height (HGT), Body weight (BW), Body surface area (BSA), Body mass index (BMI), Fat free mass (FFM), Creatinine clearance (CL_{cr}).

Where body surface area, FFM, and CLcr were calculated by using the following equations,

$$BSA[m^2] = \frac{BW^{0.425}[kg] \times HGT^{0.725}[cm] \times 71.84}{10000}$$

$$FFM(male)[kg] = \frac{9270 \times BW[kg]}{6680 + 216 \times BMI} \qquad FFM(female)[kg] = \frac{9270 \times BW[kg]}{8780 + 244 \times BMI}$$

$$CL_{CR}[mL/\min] = \frac{Creatinine_{urine}[mg/dL] \times Volume_{urine}[mL]}{Creatinine_{serum}[mg/dL] \times 1440}$$

5.3.1.2.4 METHODS:

A one-compartment model with first-order absorption and firs-order elimination (ADVAN2) was used (chosen from prior knowledge) for the population PK evaluation of LCM by using first order method (FO) in NONMEM Version IV (NONMEM Project Group, University of California, San Francisco, US)

Model selection was based on a global measure of goodness-of-fit of a model, the objective function (OBF) in NONMEM (= - 2 times the log of the likelihood of the data) was used. In addition, the goodness-of-fit of the different population models for LCM plasma concentrations was assessed by visual inspection of the following diagnostic plots:

- Observed concentrations vs. individual predicted concentrations (DV vs. IPRE)
- Observed concentrations vs. predicted concentrations (DV vs. PRED)
- Weighted residuals vs. predicted concentrations (WRES vs. PRED)
- Residuals vs. predicted concentrations (RES vs. PRED)
- Residuals vs. time (RES vs. time)
- Predicted concentrations and measured concentrations vs. time (PRED/DV vs. time)
- Weighted residuals vs. time (WRES vs. time)
- Individual predicted concentrations and measured concentrations vs. time (IPRE/DV vs. time)

The following criteria were used as additional criteria:

- Reduction of inter- and/or intra-individual (= residual) variability
- Reduction of the standard errors with respect to parameter estimates

- Analysis of residuals (random and uniform scatter around zero, no time dependency)

The criteria for accepting NONMEM model estimation were the following:

- A "successful minimization" statement by the NONMEM program
- Number of significant digits ≥ 3; if the number of significant digits is <3, reasons for acceptance of the NONMEM run are given.
- Estimates of THETA not close to boundary

Base model evaluation was mainly focus on the selection of residual error model (additive error model, proportional error model, and combined error model) and the inter-individual random effect (normally distributed or log-normal distributed).

Full model was developed to identify possible covariates. The full model was selected by using forward inclusion and backward elimination with the following steps:

- Graphical evaluation of the correlation between individual parameter estimates for k_e, Ka and V/f from the base model and potential covariates.
- After the graphical evaluation of the parameter-covariate relationships, each covariate was tested on each of the model parameters k_e, k_a and V/f by adding 1 covariate at a time (and removing it) and recording the resulting NONMEM OBF.
- Each of the potential covariates, starting with the "most significant" covariate (=largest OBF difference), was added to the model ("forward inclusion"). If the addition of a potential covariate caused a >3.841-point-decrease of the OBF ($p<0.05$, likelihood ratio test), the covariate was considered as a potentially significant covariate and was added to the model; otherwise, the covariate was dropped from the model. This resulted in building of the "full" model by including all potentially significant covariates.
- In the next step, each potentially significant covariate was removed from the full model individually to determine if a model with fewer parameters would describe the data ("backward stepwise elimination"). If the removal of a potentially significant covariate caused an increase in OBF of at least 7.88 points ($p<0.005$, likelihood ratio test), the covariate was retained in the "final" model; otherwise, the covariate was dropped from the model. In the last step, the residual error model was tested again.

After the base model and final model were established, no further model validation was performed by the sponsor.

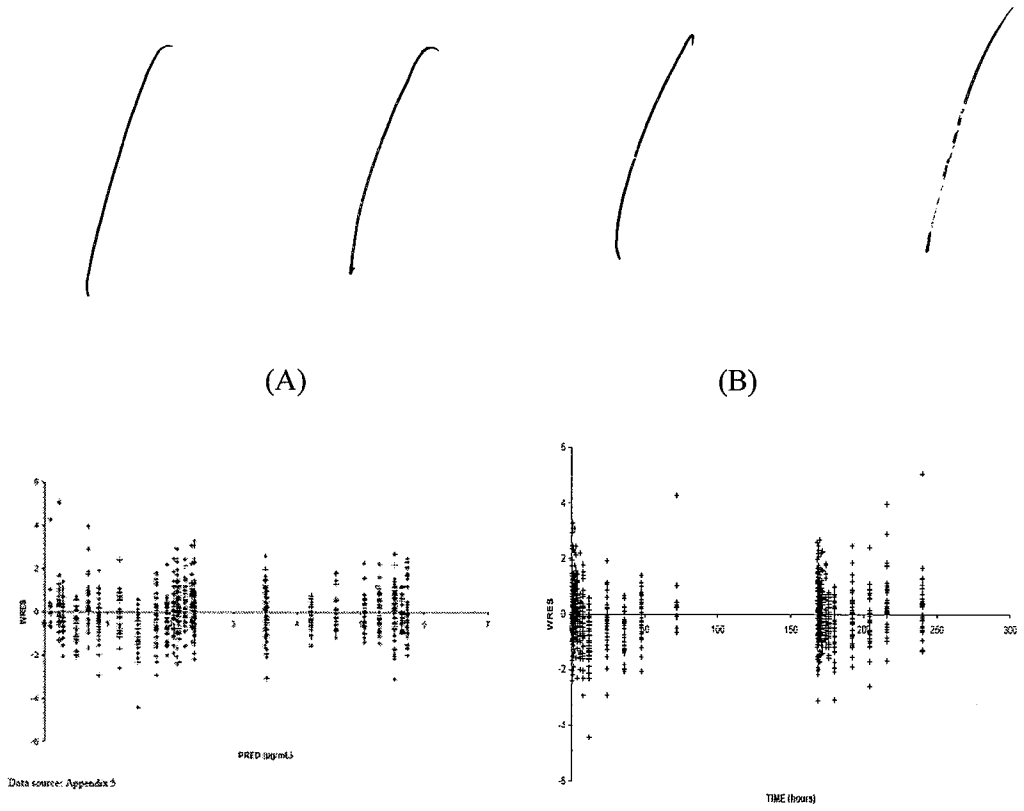
5.3.1.2.5 RESULTS:

The structure model for the final base model was one-compartment model with first-order absorption and first-order elimination, including log-normally distributed inter-individual variability on Ka, Ke, and V/f. The residual was described as the combined error model with a proportional and an additive component. The model parameter estimates were summarized in Table 4 and the major goodness-of-fit plots were shown in Figure 7.

Table 4 Lacosamide Base Population PK Model Parameter Estimates Derived from Trial SP620

Parameters	Esimates	Relative Standard Error [%]
Ka [1/hr]	3.76	14.3
Ke [1/hr]	0.0451	4.12
V/f [L]	39.6	3.56
IIV on Ka [%]	112	23.5
IIV on Ke [%]	19.2	27.1
IIV on V/f [%]	21.4	22.7
Proportional Residual Error[%]	7.91	10.8
Additive Residual Error [ug/mL]	0.0639	33.1

Figure 7 Goodness-of-fit Plots for Lacosamide Base Population PK Model Derived from Trial SP620



Note: (A) is observed versus population predicted
(B) is observed versus individual predicted
(C) is weighted residual versus population predicted

b(4)

(D) is weighted residual versus time

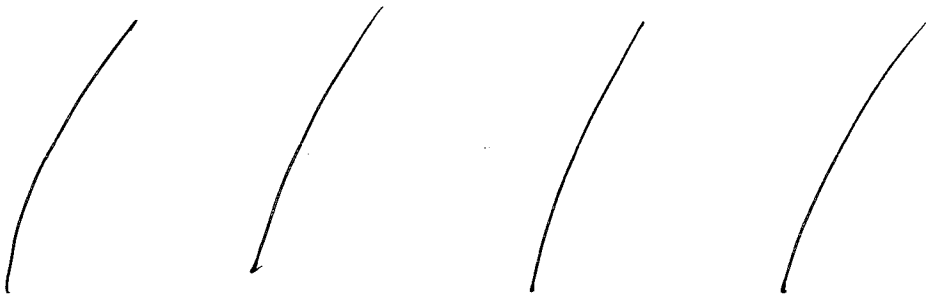
The final model was selected from the base model chosen with the same inter-individual variability and residual error structure. The covariate effect and parameter estimates were summarized in Table 5. Goodness-of-fit plots were shown in Figure 8.

Table 5 Lacosamide Final Population PK Model Parameter Estimates Derived from Trial SP620

Parameters	Estimates	RSE* [%]
Ka [1/hr]	Ka = θ1 + θ7×FFM	not applicable
θ1	2.93×10^{-6}	not applicable
θ7	0.0737	30.3
Ke [1/hr]	Ke = θ3 + θ5×CLcr + θ6×(31-BMI)	not applicable
θ3	0.0225	21.1
θ5	0.000193	30.3
θ6	0.00123	31.1
V/f [L]	V/f = θ2 + θ4×FFM	not applicable
θ2	8.18	31.2
θ4	0.612	8.97
IIV on Ka [%]	121	25.1
IIV on Ke [%]	13.7	18.8
IIV on V/f [%]	9.6	25.4
Proportional Residual Error [%]	8.01%	8.08
Additive Residual Error [ug/mL]	0.054	34.9

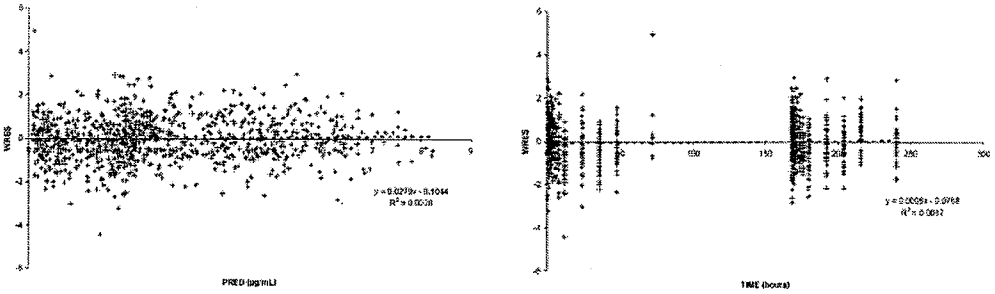
Note: *: RSE = Relative Standard Error

Figure 8 Goodness-of-fit Plots for Lacosamide Final Population PK Model Derived from Trial SP-620



(A) (B)

b(4)



(C) (D)

NOTE: (A) is observed versus population predicted
(B) is observed versus individual predicted
(C) is weighted residual versus population predicted
(D) is weighted residual versus time

5.3.1.2.6 CONCLUSIONS:

LCM plasma concentrations were adequately described by a 1-compartment model with first order absorption and first-order elimination. Overall, the mean PK parameter estimates for k_a, k_e and V/f in the target population of healthy subjects of different age and gender were comparable with those determined in other Phase 1 trials (by non-compartmental PK analysis).

- Based on the low IIV of PK parameters of lacosamide (IIV=9.6% for V/f, IIV=13.7% for k_e), it can be concluded that LCM plasma concentrations are highly predictable in the currently evaluated population. As inter-individual variability of LCM plasma concentrations is a priori low, there is not much variability in LCM plasma concentrations that have to be explained by possible covariates.
- According to the criteria specified for covariate selection, FFM was identified as covariate on V/f and k_a among the tested covariates (age, sex, body weight, FFM, height, CL_{cr}, BMI, BSA). CL_{cr} and BMI were identified as covariates on k_e.
- FFM as covariate explained approximately half of IIV of V/f (11.8% of 21.4%). The identification of FFM as covariate on V/f indicates that the most accurate prediction of V/f of subjects can be done based on FFM (and not based on body weight or other tested covariates) of the subjects. A greater FFM results in a higher V/f which implicates lower LCM plasma concentrations. Furthermore, FFM was found as a covariate on k_a (significant improvement of objective function). However, FFM could not explain the IIV of k_a more sufficiently.
- CL_{cr} and BMI as covariates could only explain a small part (5.5%) of IIV of k_e. However, the results show that elimination of LCM is influenced by CL_{cr} and BMI as a prolonged $t_{1/2}$ (=slower elimination) of LCM is observed with decreasing CL_{cr} and increasing BMI of the subjects. A result of this will be higher LCM plasma concentrations in subjects with a decreased renal function and also in subjects with higher BMI values.

- The observed differences in the pharmacokinetics of subjects with different age and sex in trial SP620 could be more adequately described by differences in FFM and CL_{cr}.
- A very good prediction of individual LCM plasma concentration profile is possible using the population PK model evaluated in the current analysis. The only parameters necessary for the individual prediction are body weight, height, age, sex and serum creatinine to calculate BMI, FFM and CL_{cr}.

3.2.2 Population PK analysis in patients with partial seizure

The sponsor submitted 2 population PK analyses reports for patients with partial seizure.

3.2.2.1 Population Pharmacokinetics of Lacosamide in Subjects with Partial Seizures with or without Secondary Generalization, Trial Number: SP755

5.3.2.1.1 OBJECTIVES:

Objectives of the population PK analysis were the following:
1. To describe population PK characteristics (i.e., typical mean PK parameters) of LCM and to characterize the inter- and intra-individual variability of the PK parameters of LCM in subjects with partial seizures with or without secondary generalization.
2. To quantify the relationship between different subject-specific factors (i.e., possible covariates as age, body weight, creatinine clearance, concomitant antiepileptic drugs [AEDs]) and PK parameters (apparent volume of distribution [V/f], rate constant of elimination [ke]).

5.3.2.1.2 CLINICAL STUDY OVERVIEW:

The Population PK analyses were performed based on clinical data obtained from trial SP755 in patients with diabetic neuropathy. Detailed information with regard to the study design can be found in section 4.2.1.

A total of 584 subjects were screened for this trial. A total of 546 subjects were enrolled in the trial and comprised the ES; 32 subjects were screen failures and 6 subjects denoted as Baseline failures did not meet all Screening criteria and were excluded from the count of enrolled subjects. Of the 546 enrolled subjects, 485 were randomized. All of the 485 randomized subjects received at least 1 dose of trial medication and comprise the Safety Set, 322 out of these 485 subjects were treated with LCM.

Trial medication was administered orally twice daily (at approximately 12 hour intervals, once in the morning and once in the evening). Plasma concentrations of LCM and concomitant AEDs were obtained in order to investigate 1) the plasma concentration of LCM, 2) whether LCM has any effect on the steady-state plasma concentration of concomitant AEDs, and 3) the correlation between LCM plasma concentrations and efficacy. In addition, a population PK analysis of LCM plasma concentrations was performed.

LCM plasma samples were obtained at the following visits:
Baseline Phase
• Visit 3 (Week 0, end of Baseline Phase)
Titration Phase
• Visit 4 (Week 2, Titration Phase)
• Visit 5 (Week 4, Titration Phase)

Maintenance Phase
• Visit 6 (Week 8, Maintenance Phase)
• Visit 8 (Week 16, Maintenance Phase)
• Early Withdrawal Visit (For subjects who discontinue from the trial between Visit 3 but before completing Visit 8)
• Unscheduled Visit (At any time during the trial, eg, due to an adverse event requiring followup)
At Visit 3, plasma sampling was planned to be done prior to dosing of trial medication (blank sample) along with hematology samples. For the rest of the visits, plasma sampling was planned to be done at any time after dosing of trial medication on that day along with hematology samples.

5.3.2.1.3 DATA FOR ANALYSIS:
2676 concentration records from 491 subjects were obtained from the study. Concentrations from some of the subjects were excluded as described below.

1. The following records were a priori not usable for population PK analysis and had to be excluded from the NONMEM analysis file because concentration records were <LOQ, samples could not be identified or details on the samples required for analysis were missing (e.g., missing sampling/dosing information):
• **Records <LOQ or unexpected concentration records relative to LOQ:**
- All 912 records from 163 placebo subjects were excluded; the majority of concentrations (782 out of 912 records) were below the LOQ. Of the 130 records >LOQ, 125 records were in the Transition Phase of the trial, where the subjects were transitioned to LCM, and therefore can be considered as plausible; however, these records were also not included in the analysis. 5 out of 130 records >LOQ were between Visit 2 and Visit 8 of the trial and were expected to be <LOQ.
- 204 LOQ records from subjects in the verum group were excluded. 154 out of the 204 records were at Visit 4 in the 200mg/day LCM group were no measurable LCM concentrations were expected due to the planned titration scheme. The rest of the records (50 records) were records in the 200mg/day and 400mg/day LCM group between Visit 4 and Visit 8 or during Transition/Taper Phase and the majority of them were expected to have measurable LCM concentrations.
- 327 predose (blank) records at Visit 3 were excluded. all were below the LOQ, with exception of 3 records in the 400mg/day LCM group that were >LOQ
- 2 records >LOQ at Visit 4 were excluded in the 200mg/day LCM group, the subjects were expected to have measurable LCM concentrations not earlier than Visit 5.
• **Records with no reported concentration results:**
For 43 records in the 200mg/day and 400mg/day LCM group, no concentration results were available and therefore, no concentration records could be included in the analysis.
• **Concentration records excluded due to missing/inadequate documentation of sampling details:**
- 4 records with missing information on time after administration were excluded.
- 12 records with negative time after administration were excluded.
- 21 records with time after administration >24hours were excluded. Per documentation, the PK sampling was done >24h after administration of trial medication and the records

were deleted because of the probability of errors in the recording of the dosing history or the time of sampling.
- 10 records were excluded because the information on the latest dose prior to PK sampling was missing.
- 97 records were excluded because the correct dosing data (with regard to individual morning and evening doses) was not determinable within 3 days prior to PK sampling.
2. The following records were excluded based on their poor dosing compliance or because they were considered as outliers:
- 16 records of 7 subjects were excluded because of a documented compliance of <75% or because of other compliance violations. The records were deleted because of the probability of errors in the recording of the dosing history.
- 20 records were excluded because the measured LCM concentration was less than 1/3 or more than 3-fold higher compared to the expected LCM concentration based on the documented dose.

Finally, 1008 concentration records from 292 subjects (out of 322 subjects randomized and treated with LCM) were used for the population PK analysis and were part of the NONMEM analysis file. This corresponds to a mean of approximately 3.5 concentration records per subject.

Following variables were included in the analyses for the selection of covariate effect: Age, Sex (Sex=0 for males, Sex=1 for females), Body weight, Height, Body mass index (BMI), Lean body weight (LBW), Creatinine clearance (CLcr), Aspartate aminotransferase (AST), Alanine aminotransferase (ALT), Gamma-glutamyltransferase (GGT), Alkaline phosphatase (ALK), Total bilirubin.

Where CLcr was estimated based on Cockcroft-Gault formula. BMI and LBW were calculated by using the following formula respectively.

$$BMI = \frac{Body\ weight(kg)}{(Height(m))^2}$$

$$\text{LBW (kg) in males} = 1.10 \cdot weight(kg) - 0.0128 \cdot BMI \cdot weight(kg)$$

$$\text{LBW (kg) in females} = 1.07 \cdot weight(kg) - 0.0148 \cdot BMI \cdot weight(kg)$$

Concomitant AEDs and AED combinations were also included as part of covariate analyses:
- conAED No. 1: Carbamazepine alone
- conAED No. 2: Carbamazepine + topiramate
- conAED No. 3: Carbamazepine + lamotrigine
- conAED No. 4: Carbamazepine + valproate
- conAED No. 5: Oxcarbazepine alone
- conAED No. 6: Carbamazepine + levetiracetam
- conAED No. 7: Valproate + topiramate
- conAED No. 8: Valproate + lamotrigine

- conAED No. 9: Carbamazepine alone or in combination with lamotrigine or levetiracetam
- conAED No. 10: Oxcarbazepine alone or in combination with 1 or 2 other AEDs1
- conAED No. 11: Carbamazepine alone or in combination with 1 or 2 other AEDs1
- conAED No. 12: Lamotrigine alone or in combination with 1 or 2 other AEDs1
- conAED No. 13: Levetiracetam alone or in combination with 1 or 2 other AEDs1
- conAED No. 14: Phenobarbital alone or in combination with 1 or 2 other AEDs1
- conAED No. 15: Phenytoin alone alone or in combination with 1 or 2 other AEDs1
- conAED No. 16: Topiramate alone or in combination with 1 or 2 other AEDs1
- conAED No. 17: Valproate alone or in combination with 1 or 2 other AEDs1

1: "1 or 2 other AEDs" includes carbamazepine, topiramate, lamotrigine, valproate, levetiracetam, clonazepam, oxcarbazepine, phenobarbital, phenytoin, gabapentin

5.3.2.1.4 METHODS:

As a global measure of the goodness-of-fit of a model, the OBF in NONMEM (i.e., - 2 times the log of the likelihood of the data) was used. In addition, the goodness-of-fit of the different population models for LCM plasma concentrations was assessed by visual inspection of the following diagnostic plots:

• Individual predicted concentrations vs. observed concentrations (IPRE vs. DV)
• Predicted concentrations vs. observed concentrations (PRED vs. DV)
• Weighted residuals vs. predicted concentrations (WRES vs. PRED)
• Residuals vs. predicted concentrations (RES vs. PRED)
• Residuals vs. time (RES vs. time)
• Predicted concentrations and observed concentrations vs. time (PRED/DV vs. time)
• Weighted residuals vs. time (WRES vs. time)
• Individual predicted concentrations and measured concentrations vs. time (PRED/DV vs. time)

The following criteria were used as additional criteria:

• Reduction of inter- and/or intra-individual
• Reduction of the standard errors with respect to parameter estimates
• Analysis of residuals (random and uniform scatter around zero, no time dependency)

The criteria for accepting NONMEM model estimation were the following:

• A "successful minimization" statement by the NONMEM program
• Number of significant digits ≥3; if the number of significant digits was <3, reasons for acceptance of the NONMEM run were given.
• Estimates of THETA (the fixed effect-parameter in NONMEM) not close to boundary

5.3.2.1.5 RESULTS:

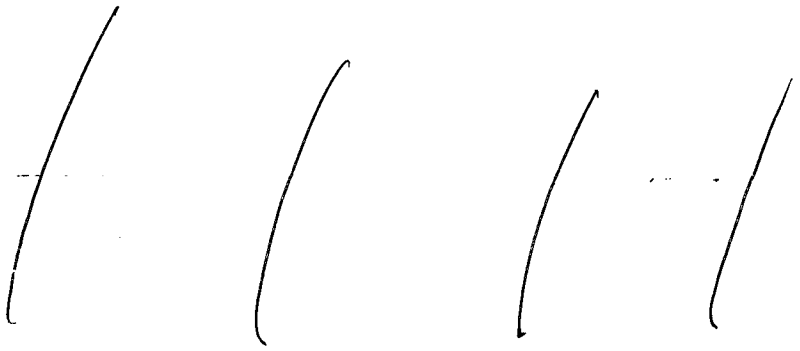
The structure model for the final base model was one-compartment model with first-order absorption and first-order elimination, including log-normally distributed inter-individual variability on Ka, Ke, and V/f. The residual was described as the combined error model with a proportional and an additive component. The major pharmacokinetic parameters were summarized in Table 6, with the goodness-of-fit plots were shown in Figure 9.

Table 6 Lacosamide Base Population PK Model Parameter Estimates Derived from Trial SP755

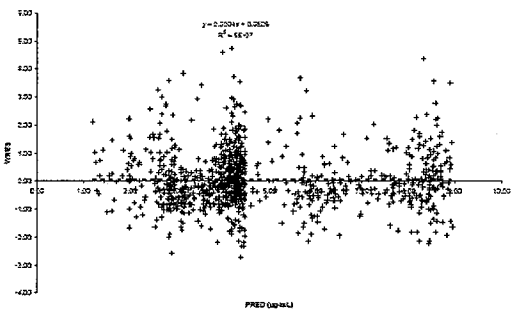
Parameter	Final estimate	RSE (%)
k_e (h^{-1})[a]	0.0357	10.1
V/f (L)	62.1	10.4
k_a (h^{-1})	4.0 (fixed)	n.a.
Parameter	**IIV (%)**	**RSE (%)**
k_e (h^{-1})	18.9	45.7
V/f (L)	16.9	56.1
k_a (h^{-1})	n.a.	n.a.
Residual error	**Final estimate**	**RSE (%)**
Proportional	22.7%	15.7
Additive	0.482µg/mL	45.3

RSE(%)= percent relative standard error of the estimate respective variance estimate for IIV; IIV(%)=Inter-individual variability in percent; n.a.=not applicable;
a k_e of 0.0357h^{-1} corresponds to a $t_{1/2}$ of 19.4h
Data source: Appendix 3

Figure 9 Goodness-of-fit Plots for Lacosamide Base Population PK Model Derived from Trial SP755 b(4)

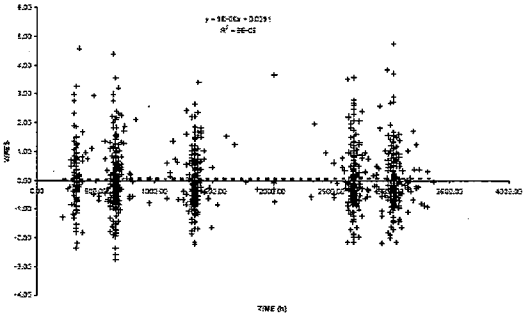


(A) (B)



Dotted line=linear regression (including equation and R^2).
Data source: Appendix 6

(C)



Dotted line=linear regression (including equation and R^2).
Data source: Appendix 6

(D)

NOTE: (A) is observed versus population predicted
(B) is observed versus individual predicted
(C) is weighted residual versus population predicted
(D) is weighted residual versus time

The final model was selected from the base model chosen with the same inter-individual variability and residual error structure. The covariate effect and parameter estimates were summarized in Table 7. Goodness-of-fit plots were shown in Figure 10.

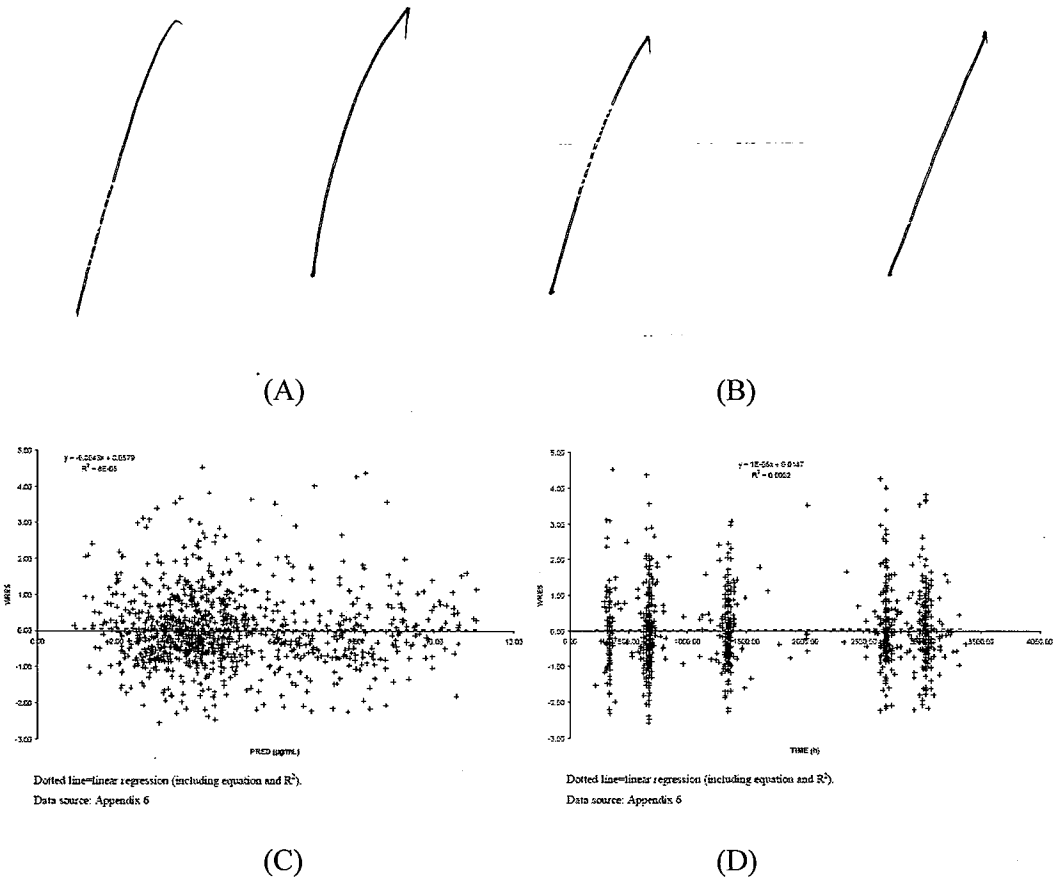
Table 7 Lacosamide Final Population PK Model Parameter Estimates Derived from Trial SP755

Parameter	Final estimate	RSE (%)
k_a (h^{-1})	$k_a = \theta 1$	n.a.
θ1	4.00 (fixed parameter)	n.a.
k_e (h^{-1})	$k_e = \theta 3 + \theta 4$ (conAED No. 11)	n.a.
θ3	0.0333	10.1
θ4	0.00795	19.5
V/f (L)	$V/f = \theta 2 + \theta 5$ (LBW – 54)	n.a.
θ2	60.0	9.93
θ5	0.495	26.7
Parameter	**IIV (%)**	**RSE (%)**
k_e (h^{-1})	19.1	37.2
V/f (L)	6.57	313%
Residual error	**Final estimate**	**RSE (%)**
Proportional	23.2%	15.2
Additive	0.439µg/mL	46.6

RSE(%)=the percent relative standard error of the estimate resp. variance estimate for IIV; IIV(%)=Inter-individual variability in percent; θ1=typical value of k_a; θ3=typical value of k_e without effect of covariate; θ2=typical value of V/f without effect of covariate; θ4=slope of the effect of covariate conAED No. 11 on k_e; θ5=slope of the effect of covariate LBW on V/f; n.a.= not applicable; LBW=lean body weight; conAED No. 11 =coadministered carbamazepine alone or in combination with 1 or 2 other AEDs; Data source: Appendix 3, Appendix 7

Figure 10 Goodness-of-fit Plots for Lacosamide Final Population PK Model Derived from Trial SP775

b(4)



NOTE: (A) is observed versus population predicted
(B) is observed versus individual predicted
(C) is weighted residual versus population predicted
(D) is weighted residual versus time

5.3.2.1.6 CONCLUSIONS:

- LCM plasma concentrations were adequately described by a 1-compartment model with first -order absorption and first-order elimination.
- Overall, the mean population PK parameter estimates for ke and V/f in the target population of subjects with partial seizures with and without secondary generalization were comparable with those determined in Phase 1 trials in healthy subjects. Inter-individual variability (IIV) of V/f in the target population (6.6%) was determined to be lower compared to the IIV (measured as CV) observed in healthy subjects in Phase 1 trials (20%). The IIV of the rate constant of elimination (ke) was comparable to the CV observed in Phase 1 trials (IIV of 19.1% in the examined target population compared to CV of 20% in healthy subjects).

- Overall, based on the observed low IIV of PK parameters of LCM (IIV=6.6% for V/f, IIV=19.1% for ke), it can be concluded that LCM plasma concentrations are predictable with good precision in the currently evaluated target population.
- According to the criteria specified for covariate selection, lean body weight (LBW) was identified as covariate on V/f and coadministration of carbamazepine alone or in combination with 1 or 2 other AEDs (topiramate, lamotrigine, valproate, levetiracetam, clonazepam, oxcarbazepine, phenobarbital, phenytoin, gabapentin) was identified as covariate on ke.
- Based on the final model results, the major determinant for V/f was the subjects' LBW. This means that V/f and therefore LCM plasma concentrations can be best predicted based on subjects' LBW. An increase in the fat-free mass by 20% in a subject results in an increase in V/f of 10% and therefore in 10% lower LCM plasma concentrations.
- Based on the final model results, elimination of LCM (characterized by rate constant of elimination, ke) is influenced by the coadministration of carbamazepine alone or in combination with 1 or 2 other AEDs. In the presence of carbamazepine (alone or in combination with 1 or 2 other AEDs), elimination of LCM was observed to be faster in the examined population (t1/2 of 16.8h compared to t1/2 of 20.8h, ie, -25%) resulting in approximately 15% lower LCM concentrations (Cmax,ss) at steady state. Therefore, based on the final model results, it can not be excluded that lower LCM plasma concentrations are observed under coadministration with carbamazepine alone or in combination with 1 or 2 other AEDs (topiramate, lamotrigine, valproate, levetiracetam, clonazepam, oxcarbazepine, phenobarbital, phenytoin, gabapentin).
- None of the other tested covariates (age, sex, body weight, height, CLcr, BMI, AST, ALT, GGT, ALK, total bilirubin, were identified as additional covariates on V/f or ke based on the specified criteria for covariate testing.
- None of the other tested concomitant AEDs or AED combinations (including topiramate, lamotrigine, valproate, levetiracetam, oxcarbazepine, phenobarbital, and phenytoin) were identfied as covariates on LCM kinetics, ie, these AEDs or AED combinations provided no clear signal of an influence on LCM kinetics in the current evaluation although an influence can not be excluded.

3.2.2.2 Population Pharmacokinetics of Lacosamide in Subjects with Partial Seizures with or without Secondary Generalization, Trial Number: SP754

5.3.2.2.1 OBJECTIVES:
Objectives of the population PK analysis were the following:
1. To describe population PK characteristics (i.e., typical mean PK parameters) of LCM and to characterize the inter- and intra-individual variability of the PK parameters of LCM in subjects with partial seizures with or without secondary generalization.
2. To quantify the relationship between different subject-specific factors (i.e., possible covariates as age, body weight, creatinine clearance, concomitant antiepileptic drugs [AEDs]) and PK parameters (apparent volume of distribution [V/f], rate constant of elimination [ke]).

5.3.2.2.2 CLINICAL STUDY OVERVIEW:
The Population PK analyses were performed based on clinical data obtained from trial SP754 in patients with diabetic neuropathy. Detailed information with regard to the study design can be found in section 4.2.1.

A total of 556 subjects were screened for this trial. A total of 489 subjects were enrolled in the trial and comprised the enrolled set; 54 were screen failures. Of the 489 enrolled subjects, 405 were randomized. All the 405 randomized subjects received at least 1 dose of trial medication and comprise the SS.

LCM plasma samples were obtained at the following visits:
Baseline Phase
• Visit 3 (Week 0, end of Baseline Phase)
Treatment Phase
• Visit 4 (Week 2, Titration Phase)
• Visit 5 (Week 4, Titration Phase)
• Visit 6 (Week 6, Titration Phase)
• Visit 7 (Week 10, Maintenance Phase)
• Visit 9 (Week 18, Maintenance Phase)
• Transition Visit 1 (Week 20, Transition Phase)
• Taper Visit 1 (Week 20, Taper Phase)
• Early Withdrawal Visit (For subjects who discontinue from the trial between Visit 3 but before completing Visit 9)
• Unscheduled Visit (At any time during the trial, eg, due to an adverse event requiring follow up)

The following parameters were used in the evaluation of possible covariates: Age, Sex (Sex=0 for males, Sex=1 for females), Race, Body weight, Height, Body mass index (BMI), Lean body weight (LBW), Creatinine clearance (CLcr), Aspartate

aminotransferase (AST), Alanine aminotransferase (ALT), Gamma-glutamyltransferase (GGT), Alkaline phosphatase (ALK), and Total bilirubin.

Specifically, the effect of the presence or absence of concomitatnt AED or AED combination was tested.

A prerequisite for the examination of an influence of concomitant AEDs is that the number of subjects co-medicated with an AED or AED combination is sufficient: if at least 10 subjects (i.e., 3.6%) are co-medicated with a specific AED or AED combination, the influence will be tested. In addition, combinations of specific AEDs or AED combinations and unspecific AED combinations were tested. Finally, the following concomitant AED or AED combinations were included in the analysis:
- conAED No. 1: Lamotrigine + levetiracetam
- conAED No. 2: Carbamazepine
- conAED No. 3: Levetiracetam
- conAED No. 4: Carbamazepine + levetiracetam
- conAED No. 5: Lamotrigine
- conAED No. 15: Carbamazepine alone or in combination with lamotrigine or levetiracetam
- conAED No. 16: Phenytoin alone or in combination with lamotrigine or levetiracetam
- conAED No. 17: Oxcarbazepine in combination with lamotrigine or levetiracetam
- conAED No. 18: Lamotrigine alone or levetiracetam alone or combination of both
- conAED No. 19: Oxcarbazepine alone or in combination with 1 or 2 other AEDs*
- conAED No. 20: Carbamazepine alone or in combination with 1 or 2 other AEDs*
- conAED No. 21: Lamotrigine alone or in combination with 1 or 2 other AEDs*
- conAED No. 22: Levetiracetam alone or in combination with 1 or 2 other AEDs*
- conAED No. 23: Phenobarbital alone or in combination with 1 or 2 other AEDs*
- conAED No. 24: Phenytoin alone or in combination with 1 or 2 other AEDs*
- conAED No. 25: Topiramate alone or in combination with 1 or 2 other AEDs*
- conAED No. 26: Valproate alone or in combination with 1 or 2 other AEDs*
- conAED No. 27: Zonisamide alone or in combination with 1 or 2 other AEDs*

* "1 or 2 other AEDs" includes carbamazepine, topiramate, lamotrigine, valproate, levetiracetam, zonisamide, oxcarbazepine, phenobarbital, phenytoin, gabapentin

5.3.2.2.3 DATA FOR ANALYSIS:

The population PK analysis was preformed based on a total of 1322 concentration records from 278 subjects (out of 301 subjects randomized and treated with LCM). The analysis of the plasma samples was performed with a validated high performance liquid chromatography with electrospray ionization triple stage mass spectrometry (LC-MS/MS) method, with the LOQ of 0.05µg/mL. From trial SP754, 2584 concentration observations from 411 subjects were recorded. Of the 411 subjects, 405 were randomized and 6 were not randomized. A subset of plasma concentration records of LCM was excluded as described below.

1. The following records were a priori not usable for population PK analysis and had to be excluded from the NONMEM analysis file because concentration records were <LOQ, samples could not be identified or details on the samples required for analysis were missing (e.g., missing sampling/dosing information):
   - **Records <LOQ or unexpected concentration records relative to LOQ:** All 697 records from 104 placebo subjects were excluded; the majority of concentrations (613 out of 697 records) were below the LOQ. Of the 84 records >LOQ, 82 records were in the Transition Phase of the trial, where the subjects were transitioned to LCM, and therefore can be considered as plausible; however, these records were also not included in the analysis. 2 out of 84 records >LOQ were at Visit 5 of the trial and were expected to be <LOQ.
     - 56 LOQ records from 46 subjects in the verum group were excluded. 22 out of the 56 records were at the end of the Taper Phase were no measurable LCM concentrations were expected due to the planned titration scheme. The rest of the records (34 records) were records between Visit 4 and Visit 8 or during Transition/Taper Phase and the majority of them were expected to have measurable LCM concentrations. For details on implausible concentration results please refer to Section 10.1.1 of the SP754 CTR.
     - 309 predose (blank) records at Visit 3 (or unscheduled Visit 1 or 2) from 294 subjects were excluded, all were below the LOQ, with exception of 7 records at unscheduled Visit 3, which were postdose and expected to be >LOQ and 6 predose records that were >LOQ.
   - **Records with no reported concentration results:** For 34 records from 32 subjects, no concentration results were available and therefore, no concentration records could be included in the analysis.
   - **Concentration records excluded due to missing/inadequate documentation of sampling details:**
     - 3 records from 3 subjects with missing information on time after administration were excluded.
     - 23 records from 21 subjects with negative time after administration were excluded.
     - 46 records from 40 subjects with time after administration >24hours were excluded. Per documentation, the PK sampling was done >24h after administration of trial medication and the records were deleted because of the probability of errors in the recording of the dosing history or the time of sampling.
     - 6 records from 5 subjects were excluded because the information on the latest dose prior to PK sampling was missing.
     - 42 records from 37 subjects were excluded because the correct dosing data (with regard to individual morning and evening doses) was not determinable within 3 days prior to PK sampling.
2. The following records were excluded based on subjects poor dosing compliance or because the records were considered as outliers:

- 26 records of 8 subjects were excluded because of a documented trial medication compliance of <75% (1 subject) or because of other compliance violations (7 subjects with major protocol deviations regarding compliance). The records were deleted because of the probability of errors in the recording of the dosing history.
- 20 records from 16 subjects were excluded because the measured LCM concentration was less than 1/3 or more than 3-fold higher compared to the expected LCM concentration based on the documented dose.

5.3.2.2.4 METHODS:

A one-compartment model with first-order absorption and first-order elimination (ADVAN2) was used (chosen based on prior knowledge) for the population PK evaluation of LCM by using first order conditional method (FOCE) in NONMEM version IV (NONMEM Project Group, University of California, San Francisco, US).

Model selection was based on a global measure of the GOF of a model, the objective function (OBF) in NONMEM (i.e., - 2 times the log of the likelihood of the data) was used. In addition, the goodness-of-fit of the different population models for LCM plasma concentrations was assessed by visual inspection of the following diagnostic plots:
• Individual predicted concentrations vs. observed concentrations (IPRE vs. DV)
• Predicted concentrations vs. observed concentrations (PRED vs. DV)
• Weighted residuals vs. predicted concentrations (WRES vs. PRED)
• Residuals vs. predicted concentrations (RES vs. PRED)
• Residuals vs. time (RES vs. time)
• Predicted concentrations and observed concentrations vs. time (PRED/DV vs. time)
• Weighted residuals vs. time (WRES vs. time)
• Individual predicted concentrations and measured concentrations vs. time (PRED/DV vs. time)
The following criteria were used as additional criteria:
• Reduction of inter- and/or intra-individual
• Reduction of the standard errors with respect to parameter estimates
• Analysis of residuals (random and uniform scatter around zero, no time dependency)
The criteria for accepting NONMEM model estimation were the following:
• A "successful minimization" statement by the NONMEM program
• Number of significant digits ≥3; if the number of significant digits was <3, reasons for acceptance of the NONMEM run were given.
• Estimates of THETA (the fixed effect-parameter in NONMEM) not close to boundary.

5.3.2.2.5 RESULTS:
The structure model for the base model was one-compartment model with first-order absorption and first-order elimination, including log-normally distributed inter-individual variability on Ke and V/f. Ka was fixed to 4.0. The residual was described as the combined error model with a proportional and an additive component. The model parameter estimates were summarized in Table 9 and the major goodness-of-fit plots were shown in Figure 11.

Table 8 Overview of tested concomitant AEDs or AED combinations

conAED/AED combination No.	Concomitant AED or AED combination	No. of subjects receiving conAED/AED combination (% of total no. of subjects)
conAED No. 1	Lamotrigine + levetiracetam	16 (5.8)
conAED No. 2	Carbamazepine	14 (5.0)
conAED No. 3	Levetiracetam	12 (4.3)
conAED No. 4	Carbamazepine + levetiracetam	12 (4.3)
conAED No. 5	Lamotrigine	12 (4.3)
conAED No. 6	Oxcarbazepine + levetiracetam	8 (2.9)
conAED No. 7	Oxcarbazepine + lamotrigine	8 (2.9)
conAED No. 8	Valproate + lamotrigine	8 (2.9)
conAED No. 9	Phenytoin	7 (2.5)
conAED No. 10	Phenytoin + lamotrigine	7 (2.5)
conAED No. 11	Carbamazepine + lamotrigine	7 (2.5)
conAED No. 12	Zonisamide + lamotrigine	7 (2.5)
conAED No. 13	Valproate + Oxcarbazepine	6 (2.2)
conAED No. 14	Phenytoin + Levetiracetam	6 (2.2)
conAED No. 15	Carbamazepine alone or in combination with lamotrigine or levetiracetam	33 (11.9)
conAED No. 16	Phenytoin alone or in combination with lamotrigine or levetiracetam	20 (7.2)
conAED No. 17	Oxcarbazepine in combination with lamotrigine or levetiracetam	16 (5.8)
conAED No. 18	Lamotrigine alone or levetiracetam alone or combination of both	40 (14.4)
conAED No. 19	Oxcarbazepine alone or in combination with 1 or 2 other AEDs*	55 (19.8)
conAED No. 20	Carbamazepine alone or in combination with 1 or 2 other AEDs*	69 (24.8)
conAED No. 21	Lamotrigine alone or in combination with 1 or 2 other AEDs*	96 (34.5)
conAED No. 22	Levetiracetam alone or in combination with 1 or 2 other AEDs*	104 (37.4)
conAED No. 23	Phenobarbital alone or in combination with 1 or 2 other AEDs*	13 (4.7)
conAED No. 24	Phenytoin alone or in combination with 1 or 2 other AEDs*	54 (19.4)

conAED/AED combination No.	Concomitant AED or AED combination	No. of subjects receiving conAED/AED combination (% of total no. of subjects)
conAED No. 25	Topiramate alone or in combination with 1 or 2 other AEDs*	46 (16.6)
conAED No. 26	Valproate alone or in combination with 1 or 2 other AEDs*	45 (16.2)
conAED No. 27	Zonisamide alone or in combination with 1 or 2 other AEDs*	46 (16.6)

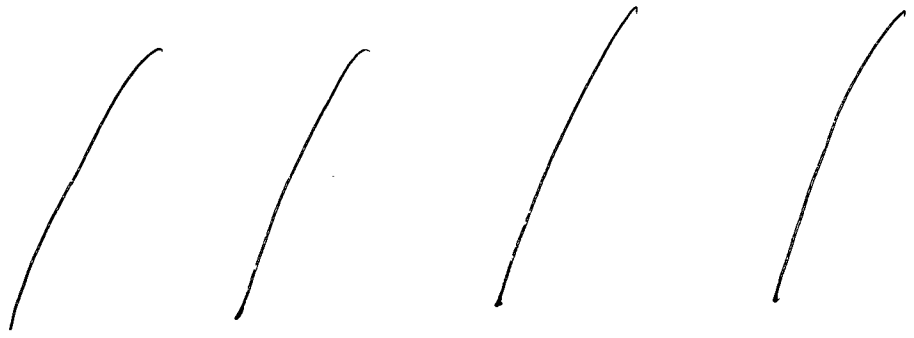
* "1 or 2 other AEDs" includes carbamazepine, topiramate, lamotrigine, valproate, levetiracetam, zonisamide, oxcarbazepine, phenobarbital, phenytoin, gabapentin
Data source: Appendix 1 (Part 2)

Table 9 Lacosamide Base Population PK Model Parameter Estimates Derived from Trial 754

Parameter	Final estimate	RSE (%)
k_e (h^{-1})[a]	0.0308	9.25
V/f (L)	72.2	9.06
k_a (h^{-1})	4.0 (fixed)	n.a.
Parameter	**IIV (%)**	**RSE (%)**
k_e (h^{-1})	20.9	24.6
V/f (L)	22.6	20.2
k_a (h^{-1})	n.a.	n.a.
Residual error	**Final estimate**	**RSE (%)**
Proportional	15.0%	15.8
Additive	0.647µg/mL	26.0

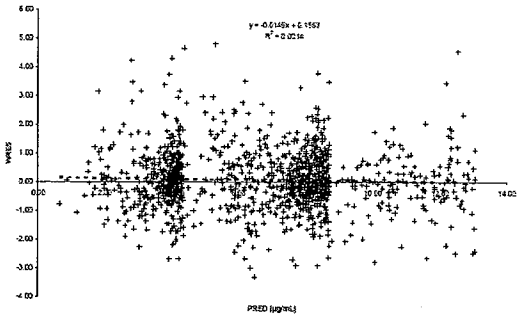
RSE(%)= percent relative standard error of the estimate respective variance estimate for IIV; IIV(%)=Inter-individual variability in percent; n.a.=not applicable;
a k_e of 0.0308h^{-1} corresponds to a $t_{1/2}$ of 22.5h
Data source: Appendix 3

Figure 11 Goodness-of-fit Plots for Lacosamide Baseline Population PK Model Derived from Trial SP754



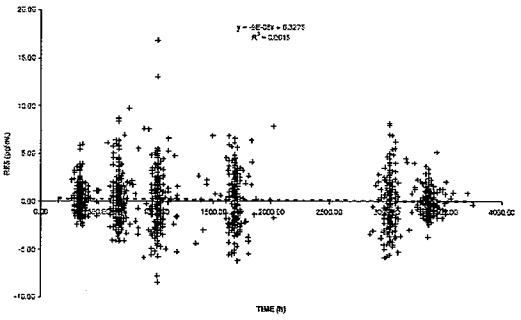
b(4)

(A) (B)



Dotted line=linear regression (including equation and R^2).
Data source: Appendix 6

(C)



Dotted line=linear regression (including equation and R^2).
Data source: Appendix 6

(D)

NOTE: (A) is observed versus population predicted
(B) is observed versus individual predicted
(C) is weighted residual versus population predicted
(D) is weighted residual versus time

The final model was selected from the base model chosen with the same inter-individual variability and residual error structure. The covariate effect and parameter estimates were summarized in Table 10. Goodness-of-fit plots were shown in Figure 12.

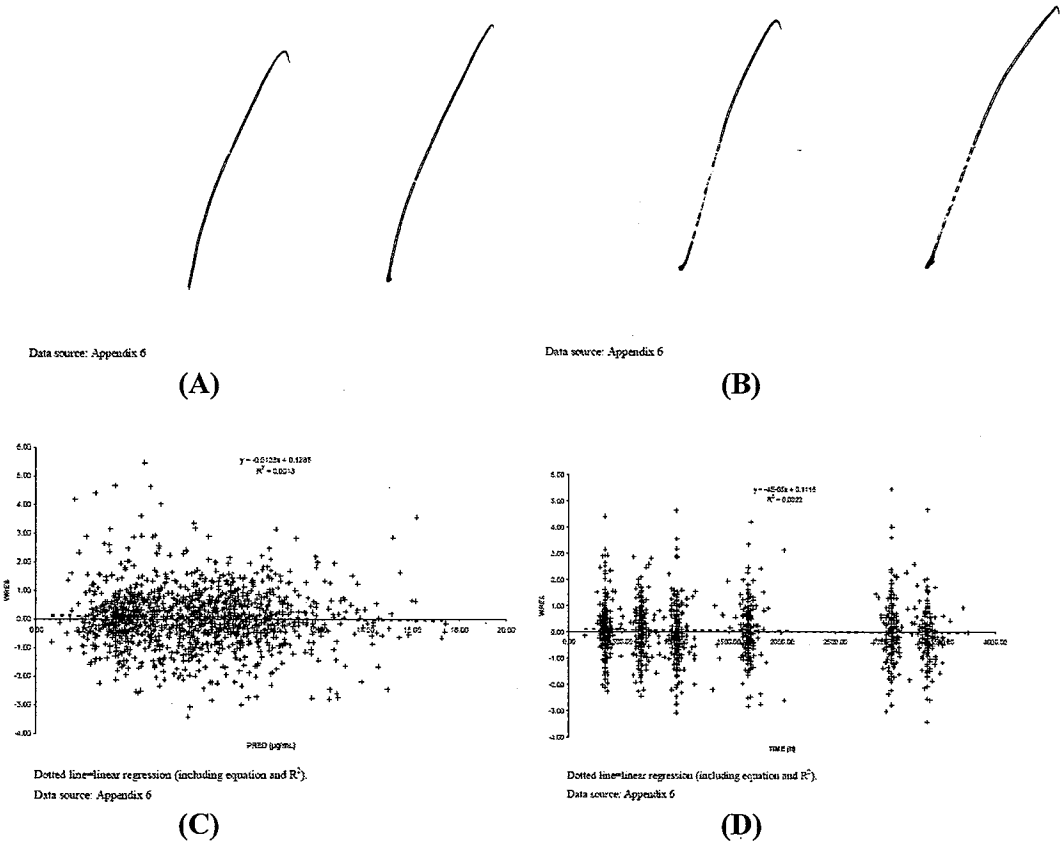
Table 10 Lacosamide Final Population PK Model Parameter Estimates Derived from Trial 754

Parameter	Final estimate	RSE (%)
k_a (h^{-1})	$k_a = \theta 1$	n.a.
θ1	4.00 (fixed parameter)	n.a.
k_e (h^{-1})	$k_e = \theta 3 + \theta 6 \times$ (conAED No. 23) + θ7 × (conAED No. 24)	n.a.
θ3	0.0290	9.79
θ6	0.0117	38.5
θ7	0.00735	30.2
V/f (L)	V/f = θ2 + θ4 × (LBW – 55.6) + θ5 × (conAED No. 20)	n.a.
θ2	68.4	9.62
θ4	0.714	16.8
θ5	19.3	17.3
Parameter	**IIV (%)**	**RSE (%)**
k_e (h^{-1})	21.4	19.9
V/f (L)	9.52	91.7
Residual error	**Final estimate**	**RSE (%)**
Proportional	14.1%	17.6
Additive	0.701µg/mL	23.4

RSE(%)=the percent relative standard error of the estimate resp. variance estimate for IIV; IIV(%)=Inter-individual variability in percent; θ1=typical value of k_a; θ3=typical value of k_e without effect of covariate; θ2=typical value of V/f without effect of covariate; θ4=slope of the effect of covariate LBW on V/f; θ5=slope of the effect of covariate conAED No. 20 on V/f; θ6=slope of the effect of covariate conAED No. 23 on k_a; θ7=slope of the effect of covariate conAED No. 24 on k_a; n.a.= not applicable; LBW=lean body weight; conAED No. 20 =coadministered carbamazepine alone or in combination with 1 or 2 other AEDs; conAED No. 23 =coadministered phenobarbital alone or in combination with 1 or 2 other AEDs; conAED No. 24 =coadministered phenytoin alone or in combination with 1 or 2 other AEDs
Data source: Appendix 3, Appendix 7

Figure 12 Goodness-of-fit Plots for Lacosamide Final Population PK Model Derived from Trial SP754

b(4)



NOTE: (A) is observed versus population predicted
(B) is observed versus individual predicted
(C) is weighted residual versus population predicted
(D) is weighted residual versus time

The sponsor performed both internal and external model validations. For internal model validation, the population PK dataset was randomly split into two subsets and used for population PK model validation. The validation was preformed by re-analyzing overall dataset and the two subsets using the final model. The results showed that the population PK parameter estimates and the residual variability were comparable for both sub-datasets and comparable with the results form analyzing the complete dataset with all subjects. For external model validation, the sponsor indicated the appropriateness of the applied one-compartment model that was used in the current evaluation of the description of SP754 LCM concentration data. In addition, the findings for V/f in the current evaluation were in agreement with the SP620 and SP640 Popoulation PK results, where V/f was best predicted based on LBW and height of subjects.

5.3.2.2.6 CONCLUSIONS:

- LCM plasma concentrations were adequately described by a 1-compartment model with first -order absorption and first-order elimination.
- Overall, the mean population PK parameter estimates for ke and V/f in the target population of subjects with partial seizures with and without secondary generalization were comparable with those determined in Phase 1 trials in healthy subjects. Inter-individual variability (IIV) of V/f in the target population (9.52%) was determined to be lower compared to the IIV (measured as CV) observed in healthy subjects in Phase 1 trials (20%). The IIV of the rate constant of elimination (ke) was comparable to the CV observed in Phase 1 trials (IIV of 21.4% in the examined target population compared to CV of 20% in healthy subjects).
- Overall, based on the observed low IIV of PK parameters of LCM (IIV=9.52% for V/f, IIV=21.4% for ke), it can be concluded that LCM plasma concentrations are predictable with good precision in the currently evaluated target population.
- According to the criteria specified for covariate selection, lean body weight (LBW) and coadministration of carbamazepine alone or in combination with 1 or 2 other AEDs (topiramate, lamotrigine, valproate, levetiracetam, zonisamide, oxcarbazepine, phenobarbital, phenytoin, gabapentin) were identified as covariates on V/f and coadministration of phenobarbital alone or in combination with 1 or 2 other AEDs and coadministration of phenytoin alone or in combination with 1 or 2 other AEDs were identified as covariates on ke.
- Based on the final model results, the major determinant for V/f was the subjects' LBW. This means that V/f and therefore LCM plasma concentrations can be best predicted based on subjects' LBW. An increase in the fat-free mass by 20% in a subject results in an increase in V/f of 12% and therefore in 12% lower LCM plasma concentrations.
- Based on the final model results, the total body clearance of LCM (CL/f) is influenced by the coadministration of carbamazepine alone or in combination with 1 or 2 other AEDs, by the coadministration of phenobarbital alone or in combination with 1 or 2 other AEDs and by the coadministration of phenytoin alone or in combination with 1 or 2 other AEDs. In the presence of carbamazepine, phenobarbital or phenytoin (alone or in combination with 1 or 2 other AEDs), CL/f was observed to be higher in the examined population (CL/f of 2.54L, 2.78L, or 2.49L compared to CL/f of 1.98L, ie, -28%, -40% or -25%, respect.) resulting in somewhat lower LCM concentrations (Cmax,ss) at steady state (-20%, -24%, -17%, respect.). Therefore, based on the final model results, it can not be excluded that lower LCM plasma concentrations are observed under coadministration with carbamazepine, phenobarbital or phenytoin alone or in combination with 1 or 2 other AEDs (topiramate, lamotrigine, valproate, levetiracetam, zonisamide, oxcarbazepine, gabapentin).
- None of the other tested covariates (age, sex, race, body weight, height, CLcr, BMI, AST, ALT, GGT, ALK, total bilirubin) were identified as additional covariates on V/f or ke based on the specified criteria for covariate testing.

3.2.3 Population PK analysis in patients with diabetic neuropathy

The sponsor submitted 3 population PK analyses reports for patients with diabetic neuropathy.

3.2.3.1 Population Pharmacokinetics of Lacosamide in Subjects with Diabetic Neuropathy, Trial Number: SP665

5.3.3.1.1 OBJECTIVE:

The objectives for population PK study of lacosamide in trial SP665 were,

1. To describe population PK characteristics (= typical mean PK parameters) of LCM and to characterize the inter- and intra-individual variability of the PK parameters of LCM in subjects with diabetic neuropathy.
2. To quantify the relationship between different subject-specific factors (= possible covariates, e.g., body weight, creatinine clearance etc.) and PK parameters (apparent volume of distribution [V/f], rate constant of elimination [K_e]).

5.3.3.1.2 CLINICAL STUDY OVERVIEW:

The Population PK analyses were performed based on clinical data obtained from trial SP665 in patients with diabetic neuropathy.

Totally 69 subjects were enrolled in the trial. Over the entire trial, the most frequently taken dose (defined as the modal dose) was 400mg/day. There were 37, 12, 13, and 7 subjects in the 400, 300, 200, and 100mg/day modal dose groups, respectively.

Lacosamide plasma samples were planned to be taken pre-dose and postdose at any time during the following visits except at Termination Visit when samples were to be taken at the time of the electrocardiogram (ECG):

Titration Phase
- Visit 2 (Month 0, Week 0)
- Additional Visits for dose escalation during Titration Phase (eg, Visit 2.1, Visit 2.x etc.) in weekly intervals (Month 0, up to Week 3)

Maintenance Phase
- Visit 3 (Month 1, Week 4)
- Visit 4 (Month 2, Week 8, 4 weeks after Visit 3)
- Visit 5 (Month 3, Week 12, 4 weeks after Visit 4)
- Visit 6 (Month 4, Week 16, 4 weeks after Visit 5)
- Visit 7 (Month 5, Week 20, 4 weeks after Visit 6)

Extension Phase
- Visit 8 (4 weeks after Visit 7; 8.1, 8.2, 8.x etc., x extension periods of 3 months)

Trial Termination
- Termination Visit

Visits 2 through 8.x were planned to take place in the morning. Subjects were instructed to delay their morning dose of trial medication until after their blood samples (hematology, blood chemistry and coagulation, and pre-dose PK sample) and ECGs (Visit 2, 2.x only) have been taken in the clinic.

5.3.3.1.3 DATA FOR ANALYSIS:

The population PK evaluation was preformed based on 1440 plasma concentrations from 69 subjects. The analysis of the plasma samples was performed with a validated liquid chromatography (LC) electrospray MS/MS method, with the LOQ was 0.05 µg/mL for all samples except for the samples of the first sequence on 02 Feb 2005. For samples of the first sequence on 02 Feb 2005, the LOQ was 0.01 µg/mL. In the trial SP665, 1564 concentrations (data points) from 69 subjects, i.e., a mean of 23 data points per subject, were recorded. 124 plasma concentrations of LCM were excluded for the following reasons:

1. 67 plasma concentrations with concentrations below the lower limit of quantification (<LOQ) at Visit 2.0, predose (before first administration of LCM) were excluded.
2. 23 plasma concentrations with concentrations <LOQ at other Visits than Visit 2.0 (predose) were excluded.
3. 21 plasma concentrations from 21 subjects were excluded because the information on time of administration of trial medication was missing; therefore, no actual time after administration could be calculated.
4. 5 plasma concentrations were excluded due to implausible concentration results for subjects 10093, 10175 and 10242:
   - Visit 2.0 (subject 10093 and subject 10175). Contrary to what was expected, the predose concentration was >LOQ, and the postdose concentration was <LOQ. An interchange of pre- and postdose sample was assumed. Therefore, the plasma concentrations of these subjects were excluded from the Population PK analysis.
   - Visit 2.0 (subject 10242): Contrary to what was expected, the postdose concentration was <LOQ. Therefore, this sample was excluded from the Population PK analysis.
5. 8 plasma concentrations from subject 10093 (all records after Day 351) were excluded because the subject apparently missed dosing for 36.5 days of the 12-week period between 13 Jan 2004 (corresponding to Day 351) and 06 Apr 2004. Therefore, approximately 50% of trial medication was apparently not taken during the 12-week period and this was the reason for the exclusion of 8 plasma concentrations of the subject (although the overall treatment compliance for this subject was estimated to be between 75% and 125%).

The following parameters were used in the evaluation of possible covariates: Age, Sex (Sex=0 for males, Sex=1 for females), Height (HGT), Body weight (BW), Body mass index (BMI), Lean body weight (LBW), Creatinine clearance (CL_{cr}), Aspartate

aminotransferase (AST), Alanine aminotransferase (ALT), Gamma glutamyltransferase (GGT), Alkaline phosphatase (AP), Total bilirubin.

Where CLcr and LBW was calculated by the following formula:

$$CL_{cr}\ [mL/\min] = \frac{(140 - age) \times weight\ [kg]}{72 - S_{creat}\ [mg/mL]}$$ If sex=female then $CL_{cr} = CL_{cr} \times 0.85$

and,

$$\text{LBW [kg] in males} = 1.10 \times weight[kg] - 0.0128 \times BMI \times weight[kg]$$

$$\text{LBW [kg] in females} = 1.07 \times weight[kg] - 0.0148 \times BMI \times weight[kg]$$

5.3.3.1.4 METHODS:

A one-compartment model with first-order absorption and firs-order elimination (ADVAN2) was used (chosen from prior knowledge) for the population PK evaluation of LCM by using first order method (FO) in NONMEM Version IV (NONMEM Project Group, University of California, San Francisco, US)

Model selection was based on a global measure of goodness-of-fit of a model, the objective function (OBF) in NONMEM (= - 2 times the log of the likelihood of the data) was used. In addition, the goodness-of-fit of the different population models for LCM plasma concentrations was assessed by visual inspection of the following diagnostic plots:

- Observed concentrations vs. individual predicted concentrations (DV vs. IPRE)
- Observed concentrations vs. predicted concentrations (DV vs. PRED)
- Weighted residuals vs. predicted concentrations (WRES vs. PRED)
- Residuals vs. predicted concentrations (RES vs. PRED)
- Residuals vs. time (RES vs. time)
- Predicted concentrations and measured concentrations vs. time (PRED/DV vs. time)
- Weighted residuals vs. time (WRES vs. time)
- Individual predicted concentrations and measured concentrations vs. time (IPRE/DV vs. time)

The following criteria were used as additional criteria:

- Reduction of inter- and/or intra-individual (=residual) variability
- Reduction of the standard errors with respect to parameter estimates
- Analysis of residuals (random and uniform scatter around zero, no time dependency)

The criteria for accepting NONMEM model estimation were the following:

- A "successful minimization" statement by the NONMEM program
- Number of significant digits ≥ 3; if the number of significant digits is <3, reasons for acceptance of the NONMEM run are given.
- Estimates of THETA not close to boundary

Base model evaluation was mainly focus on the selection of residual error model (additive error model, proportional error model, and combined error model) and the inter-individual random effect (normally distributed or log-normal distributed).

Full model was developed to identify possible covariates. The full model was selected by using forward inclusion and backward elimination with the following steps:

- Graphical evaluation of the correlation between individual parameter estimates for k_e and V/f from the base model and potential covariates.
- After the graphical evaluation of the parameter-covariate relationships, each covariate was tested on each of the model parameters k_e and V/f by adding 1 covariate at a time (and removing it) and recording the resulting NONMEM OBF.
- Each of the potential covariates, starting with the "most significant" covariate (=largest OBF difference), was added to the model ("forward inclusion"). If the addition of a potential covariate caused a >3.841-point-decrease of the OBF ($p<0.05$, likelihood ratio test), the covariate was considered as a potentially significant covariate and was added to the model; otherwise, the covariate was dropped from the model. This resulted in building of the "full" model by including all potentially significant covariates.
- In the next step, each potentially significant covariate was removed from the full model individually to determine if a model with fewer parameters would describe the data ("backward stepwise elimination"). If the removal of a potentially significant covariate caused an increase in OBF of at least 7.88 points ($p<0.005$, likelihood ratio test), the covariate was retained in the "final" model; otherwise, the covariate was dropped from the model. In the last step, the residual error model was tested again.

After building the final model, a model validation was conducted with the scope to demonstrate (in addition to the diagnostic plots) that the final model is a sufficiently good description of the data. Therefore, an internal model validation was done using the method of data splitting of the corresponding analysis file with the concentration data for NONMEM. The final model has been used for each of the datasets and the results of the 2 runs were compared with the results of the final model using the NONMEM analysis file with the concentration data of all subjects.

5.3.3.1.5 RESULTS:

The structure model for the base model was one-compartment model with first-order absorption and first-order elimination, including log-normally distributed inter-individual variability on Ke and V/f. Ka was fixed to 4.2. The residual was described as the combined error model with a proportional and an additive component. The model parameter estimates were summarized in Table 4 and the major goodness-of-fit plots were shown in Figure 7.

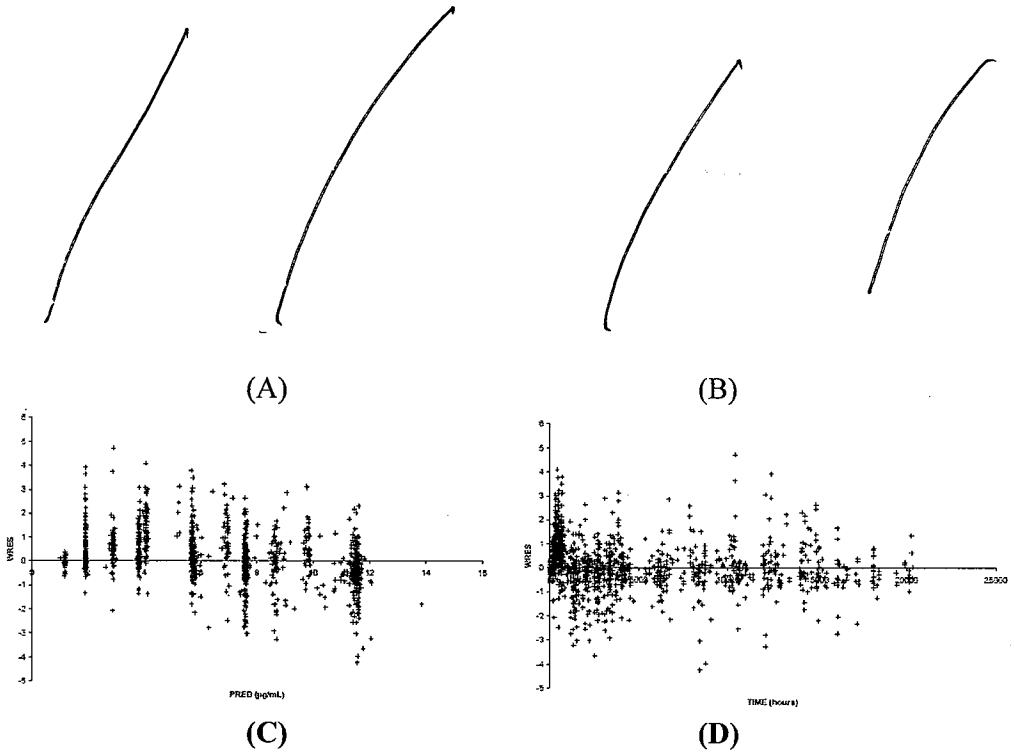
Table 11 Lacosamide Base Population PK Model Parameter Estimates Derived from Trial 665

Parameter	Final estimate	RSE [%]
k_e [h^{-1}]*	0.0431	4.22
V/f [L]	39.5	4.23
k_a [h^{-1}]	4.2	n.d.
Parameter	**IIV [%]**	**RSE [%]**
k_e [h^{-1}]	20.6	51.1
V/f [L]	19.3	44.9
k_a [h^{-1}]	n.d.	n.d.
Residual error	**Final estimate**	**RSE [%]**
Proportional	5.39%	224%
Additive	1.70µg/mL	15.2%

Data source: Appendix 3, 7

RSE[%]is the percent relative standard error of the estimate resp. variance estimate for IIV; IIV[%]=Inter-individual variability in percent; *k_a of 0.0431h^{-1} corresponds to a $t_{1/2}$ of 16.1h;

Figure 13 Goodness-of-fit for Lacosamide Base Population PK Model Derived from Trial SP 665



(A) (B)

(C) (D)

NOTE: (A) is observed versus population predicted
(B) is observed versus individual predicted
(C) is weighted residual versus population predicted

(D) is weighted residual versus time

The final model was selected from the base model chosen with the same inter-individual variability and residual error structure. The covariate effect and parameter estimates were summarized in Table 12. Goodness-of-fit plots were shown in Figure 14.

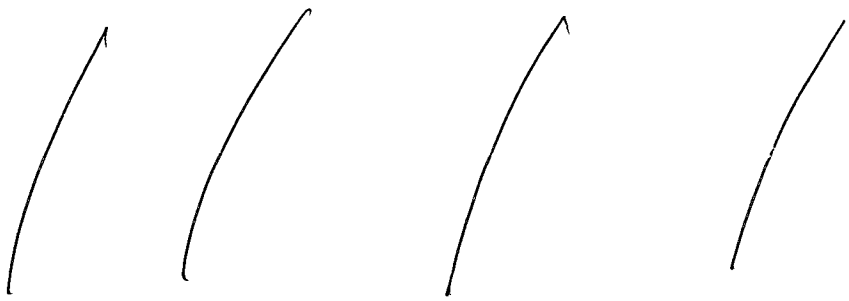
Table 12 Lacosamide Final Population PK Model Parameter Estimates Derived from Trial SP 665

Parameter	Final estimate	RSE [%]
k_a [h^{-1}]	$k_a = \theta 1$	n.d.
θ1	4.20 (fixed parameter)	n.d
k_e [h^{-1}]	$k_e = \theta 3 + \theta 5$ x (Age-59)	n.d.
θ3	0.0428	3.86
θ5	-0.000585	35.9
V/f [L]	V/f = θ2 + θ4 (Height – 1.71)	n.d.
θ2	39.6	3.56
θ4	53.1	31.6
Parameter	**IIV [%]**	**RSE [%]**
k_e [h^{-1}]	20.2	39.3
V/f [L]	14.0	82.7
Residual error	**Final estimate**	**RSE [%]**
Proportional	11.0%	61.2%
Additive	1.56µg/mL	17.5%

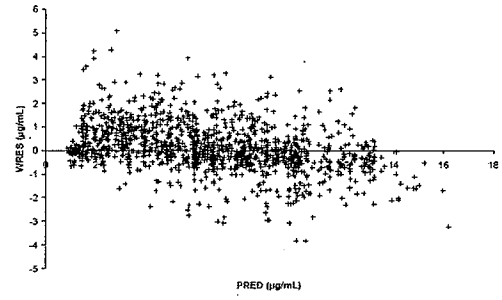
Data source: Appendix 3, 7
RSE[%]=the percent relative standard error of the estimate resp. variance estimate for IIV; IIV[%]=Inter-individual variability in percent; θ1=typical value of k_a; θ2=typical value of V/f without effect of covariate; θ4=slope of the effect of covariate height on V/f; θ3=typical value of k_e without effect of covariate; θ5=slope of the effect of covariate age on k_e;

Figure 14 Goodness-of-fit for Lacosamide Final Population PK Model Derived from Trial SP 665.

b(4)

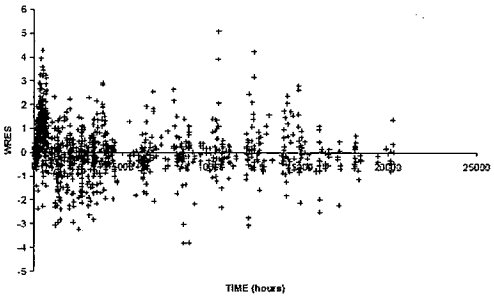


(A)



Datasource: Appendix 6

(B)



Datasource: Appendix 6

(C) (D)

NOTE: (A) is observed versus population predicted
(B) is observed versus individual predicted
(C) is weighted residual versus population predicted
(D) is weighted residual versus time

The population PK dataset was randomly split into two subsets and used for population PK model validation. The validation was preformed by re-analyzing overall dataset and the two subsets using the final model. The results showed that the population PK parameter estimates and the residual variability were comparable for both sub-datasets and comparable with the results form analyzing the complete dataset with all subjects.

5.3.3.1.6 CONCLUSIONS:

LCM plasma concentrations were adequately described by a 1-compartment model with first order absorption and first-order elimination. Overall, the mean PK parameter estimates for k_e and V/f and IIV of k_e in the target population of subjects with diabetic neuropathy were comparable with those determined in Phase 1 trials in healthy subjects.

- Based on the low IIV of PK parameters of lacosamide (IIV=14.0% for V/f, IIV=20.2% for k_e), it can be concluded that LCM plasma concentrations are highly predictable in the currently evaluated population. As variability of LCM plasma concentrations is a priori low, there is not much variability in LCM plasma concentrations that can be explained by possible covariates.
- According to the criteria specified for covariate selection, height was identified as covariate on V/f and age was identified as covariate on k_e among the tested covariates (age, sex, body, weight, LBW, height, CL_{cr}, BMI, AST, ALT, GGT, AP, and total bilirubin).
- Height as covariate explained only a small part (5.3%) of IIV of V/f. The identification of height as covariate on V/f indicates that the most accurate prediction of V/f of subjects can be done based on height (and not based on body weight or other tested covariates) of the subjects. A greater height results in a higher V/f which implicates lower LCM plasma concentrations.

- Age as a covariate could only explain a minor part (0.4%) of IIV of k_e. However, the results show that elimination of LCM is influenced by age as a prolonged $t_{1/2}$ (=slower elimination) of LCM is observed with increasing age of the subjects. A result of this will be higher LCM plasma concentrations in elderlies compared to younger subjects.

3.2.3.2 Population Pharmacokinetics of Lacosamide in Subjects with Diabetic Neuropathy, Trial Number: SP742

5.3.3.2.1 OBJECTIVES:

The objectives for the population pharmacokinetics of lacosamide in subjects with diabetic neuropathy based on trial SP742 were:

1. To describe population PK characteristics (i.e., typical mean PK parameters) of LCM and to characterize the inter- and intra-individual variability of the PK parameters of LCM in subjects with diabetic neuropathy.
2. To quantify the relationship between different subject-specific factors (i.e., possible covariates, e.g., body weight, creatinine clearance) and PK parameters (apparent volume of distribution [V/f], rate constant of elimination [k_e]).

5.3.3.2.2 CLINICAL STUDY OVERVIEW:

The Population PK analyses were performed based on clinical data obtained from trial SP742 in patients with diabetic neuropathy. Detailed information with regard to the study design can be found in section 4.2.2.

A total of 496 subjects were enrolled in this trial. Of these subjects, 370 (74.6%) were randomized, received at least 1 dose of trial medication, and were included in the Safety Set (SS). Of the 370 subjects in the SS, 93 were in the placebo group, 93 were in the 200mg/day LCM group, 91 were in the 400mg/day LCM group, and 93 were in the 600mg/day LCM group.

LCM plasma samples were obtained at all protocol-specified visits following Visit 1 where an electrocardiogram (ECG) was done:

Titration Phase
- Visit 2 (Week 1)
- Visit 3 (Week 3)
- Visit 4 (Week 5)
- Visit 5 (Week 6)

Maintenance Phase
- Visit 6 (Week 7)
- Visit 7 (Week 11)
- Visit 8 (Week 15)

Transition/Taper Phase
- Visit 9 (Week 19)
- Early Termination Visit (for subjects who prematurely discontinued)

Safety Follow-Up
- Termination Visit (for subjects who entered the open-label trial)
- Follow-Up Visit (for subjects who did not enter the open-label trial or for subjects who prematurely discontinued 14 ± 3 days after the last dose of trial medication)

All plasma samples were obtained at (or near) the same time point as the ECG. At Visit 2, a predose plasma sample was taken at the time of the third ECG and a postdose sample was taken 2 hours after dosing.

5.3.3.2.3 DATA FOR ANALYSIS:

The population PK evaluation was preformed based on 1660 concentration records from 270 subjects (i.e., a mean of approximately 6 PK samples per subject). The analysis of the plasma samples was preformed with a validated liquid chromatography (LC) electrospray mass spectrometry (MS) method, with the LOQ was 0.05µg/mL for all samples except for the reassayed samples (LOQ of 0.02µg/mL). From the trial, 3114 observations from 369 subjects (including records from placebo subjects) were recorded. Among them, the following plasma concentration records of LCM were excluded:

1. All 799 records from placebo subjects were excluded; the majority of concentrations (728 out of 799 records) were below the lower limit of quantification (<LOQ). Of the 71 records >LOQ, 67 were in the Transition Phase of the trial, and therefore might not be implausible; however, these records were also not included into the analysis.
2. 409 records <LOQ from verum subjects were excluded (248 out of these 409 records were predose samples before the first administration of trial medication at Visit 2, 261out of these 409 occurred in the titration or maintenance phase).
3. 112 records were excluded because of unclear time point of sampling with respect to the last application before sampling:
    - 25 records were excluded because of missing information about the last dose before sampling.
    - 22 records (not Visit 2, predose) were excluded because per documentation, the PK sampling was done before trial drug administration resulting in negative actual times after administration.
    - 65 records with an actual time after administration >24h were excluded. Per documentation, the PK sampling was done >24h after drug administration and the data were considered implausible.
4. 74 records were excluded because of unclear dose information before sampling. In these cases, 3 or more doses were recorded for the day of sampling, but it remained unclear which of them were given before sampling.
5. 22 records were excluded because of missing dose information before sampling (more than 3 days).
6. 23 records were excluded because of 1 or more missing doses before sampling and a recorded actual time after administration of <12 hours.
7. 2 subjects (Subject 15302 and Subject 14248) were excluded because of no recorded dose in a time frame of more than 3 days before any of the plasma concentrations (Subject 15302) or because of no recorded doses (Subject 14248).
8. 1 subject was excluded because there was different information about body weight and height for some of the visits (Subject 15218).

The following parameters were used in the evaluation of possible covariates: Age, Sex (Sex=0 for males, Sex=1 for females), Height (HGT), Body weight (BW), Body mass index (BMI), Lean body weight (LBW), Creatinine clearance (CL_{cr}), Aspartate aminotransferase (AST), Alanine aminotransferase (ALT), Gamma glutamyltransferase (GGT), Alkaline phosphatase (ALK), and bilirubin.

Where BMI, CLcr, LBW, and ideal body weight (NBW) were calculated as following:

$$BMI = \frac{Body\ weight(kg)}{(Height(m))^2}$$

$$NBW_{male} = 49.866 \cdot HGT^2 - 101.270 \cdot HGT + 91.810$$

$$NBW_{female} = 32.092 \cdot HGT^2 - 40.143 \cdot HGT + 34.885$$

$$CL_{cr}\ (mL/\min) = \frac{(140 - age) \cdot weight\ (kg)}{72 - S_{crea}\ (mg/mL)}$$

If sex=female then $CL_{cr} = CL_{cr} \times 0.85$

S_{crea}= serum creatinine

$$\text{LBW (kg) in males} = 1.10 \cdot weight(kg) - 0.0128 \cdot BMI \cdot weight(kg)$$

$$\text{LBW (kg) in females} = 1.07 \cdot weight(kg) - 0.0148 \cdot BMI \cdot weight(kg)$$

5.3.3.2.4 METHODS:

A one-compartment model with first-order absorption and firs-order elimination (ADVAN2) was used (chosen from prior knowledge) for the population PK evaluation of LCM by using first order conditional estimation method (FOCE) in NONMEM Version IV (NONMEM Project Group, University of California, San Francisco, US)

Model selection was based on a global measure of goodness-of-fit of a model, the objective function (OBF) in NONMEM (= - 2 times the log of the likelihood of the data) was used. In addition, the goodness-of-fit of the different population models for LCM plasma concentrations was assessed by visual inspection of the following diagnostic plots:

- Observed concentrations vs. individual predicted concentrations (DV vs. IPRE)
- Observed concentrations vs. predicted concentrations (DV vs. PRED)
- Weighted residuals vs. predicted concentrations (WRES vs. PRED)
- Residuals vs. predicted concentrations (RES vs. PRED)
- Residuals vs. time (RES vs. time)
- Predicted concentrations and measured concentrations vs. time (PRED/DV vs. time)
- Weighted residuals vs. time (WRES vs. time)
- Individual predicted concentrations and measured concentrations vs. time (IPRE/DV vs. time)

The following criteria were used as additional criteria:

- Reduction of inter- and/or intra-individual (=residual) variability (≥ 1.5%)
- Reduction of the standard errors with respect to parameter estimates
- Analysis of residuals (random and uniform scatter around zero, no time dependency)

The criteria for accepting NONMEM model estimation were the following:

- A "successful minimization" statement by the NONMEM program
- Number of significant digits ≥ 3; if the number of significant digits is <3, reasons for acceptance of the NONMEM run are given.
- Estimates of THETA not close to boundary

Base model evaluation was mainly focus on the selection of residual error model (additive error model, proportional error model, and combined error model) and the inter-individual random effect (normally distributed or log-normal distributed).

Full model was developed to identify possible covariates. The full model was selected by using forward inclusion and backward elimination with the following steps:

- Graphical evaluation of the correlation between individual parameter estimates for k_e and V/f from the base model and potential covariates.
- After the graphical evaluation of the parameter-covariate relationships, each covariate was tested on each of the model parameters k_e and V/f by adding 1 covariate at a time (and removing it) and recording the resulting NONMEM OBF.
- Each of the potential covariates, starting with the "most significant" covariate (=largest OBF difference), was added to the model ("forward inclusion"). If the addition of a potential covariate caused a >7.88-point-decrease of the OBF ($p<0.005$, likelihood ratio test), the covariate was considered as a potentially significant covariate and was added to the model; otherwise, the covariate was dropped from the model.
- In the next step, each potentially significant covariate was removed from the full model individually to determine if a model with fewer parameters would describe the data ("backward stepwise elimination"). If the removal of a potentially significant covariate caused an increase in OBF of at least 10.8 points ($p<0.001$, likelihood ratio test), the covariate was retained in the "final" model; otherwise, the covariate was dropped from the model.

No further model validation was preformed by the sponsor.

5.3.3.2.5 RESULTS:

The structure model for the base model was one-compartment model with first-order absorption and first-order elimination, including log-normally distributed inter-individual variability on Ke and V/f. Ka was fixed to 4.2. The residual was described as the combined error model with a proportional and an additive component. The model parameter estimates were summarized in Table 13 and the major goodness-of-fit plots were shown in Figure 15.

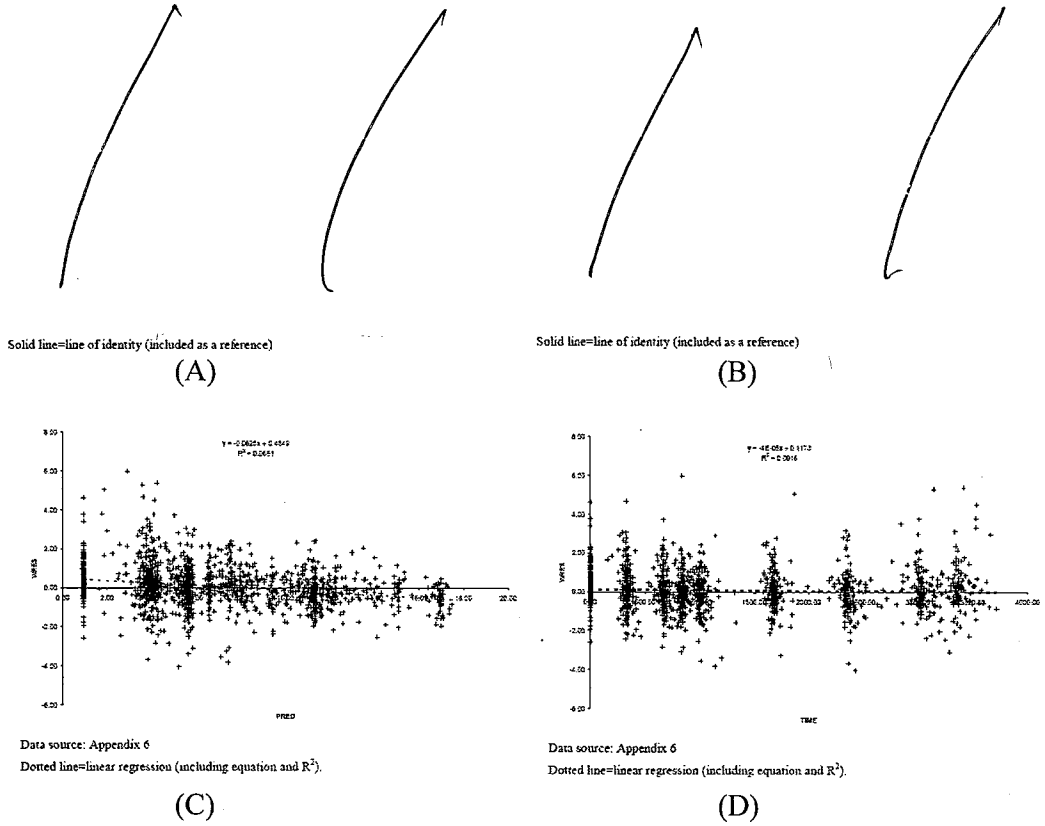
Table 13 Lacosamide Base Population PK Model Parameter Estimates Derived from Trial 742

Parameter	Final estimate	RSE (%)
k_e (h^{-1})[a]	0.0339	4.66
V/f (L)	49.7	5.15
k_a (h^{-1})	4.2	n.a.
Parameter	**IIV (%)**	**RSE (%)**
k_e (h^{-1})	21.5	18.5
V/f (L)	16.9	22.9
k_a (h^{-1})	n.a.	n.a.
Residual error	**Final estimate**	**RSE (%)**
Proportional	20.4%	9.42
Additive (µg/mL)	0.216	76.6

RSE(%)= percent relative standard error of the estimate respective variance estimate for IIV; IIV(%)=Inter-individual variability in percent; n.a.=not applicable;
[a]k_a of 0.0339h^{-1} corresponds to a $t_{1/2}$ of 20.4h;
Data source: Appendix 3

Figure 15 Goodness-of-fit for Lacosamide Base Population PK Model Derived from Trial SP742

b(4)



Solid line=line of identity (included as a reference)

(A)

Solid line=line of identity (included as a reference)

(B)

Data source: Appendix 6

Dotted line=linear regression (including equation and R^2).

(C)

Data source: Appendix 6

Dotted line=linear regression (including equation and R^2).

(D)

Note: (A) is observed versus population predicted
(B) is observed versus individual predicted
(C) is weighted residual versus population predicted
(D) is weighted residual versus time

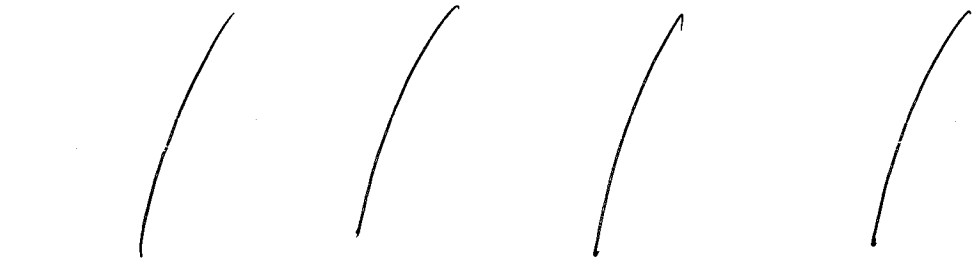
The final model was selected from the base model chosen with the same inter-individual variability structure. Unlike the residual error model structure used in the base model, the full model used proportional error structure. The covariate effect and parameter estimates were summarized in Table 14. Goodness-of-fit plots were shown in Figure 16.

Table 14 Lacosamide Final Population PK Model Parameter Estimates Derived from Trial SP742

Parameter	Final estimate	RSE (%)
k_a (h^{-1})	$k_a = \theta 1$	n.a.
θ1	4.20 (fixed parameter)	n.a.
k_e (h^{-1})	$k_e = \theta 2$	n.a.
θ2	0.0350	2.22
V/f (L)	V/f = θ3 + θ4 (HGT – 1.73) + θ5 (WGT-99.8)	n.a.
θ3	48.3	1.56
θ4	47.2	14.4
θ5	0.147	20.5
Parameter	**IIV (%)**	**RSE (%)**
k_e (h^{-1})	22.2	15.6
V/f (L)	10.1	43.4
Residual error	**Final estimate (%)**	**RSE (%)**
Proportional	21.0	7.83

RSE(%)=the percent relative standard error of the estimate resp. variance estimate for IIV; IIV(%)=Inter-individual variability in percent; θ1=typical value of k_a; θ2=typical value of k_e without effect of covariate; θ3=typical value of V/f without effect of covariate; θ4=slope of the effect of covariate height on V/f; θ5=slope of the effect of covariate weight on V/f; n.a.= not applicable; HGT=height; WGT=weight;
Data source: Appendix 3, Appendix 7

Figure 16 Goodness-of-fit for Lacosamide Final Population PK Model Derived from Trial SP742

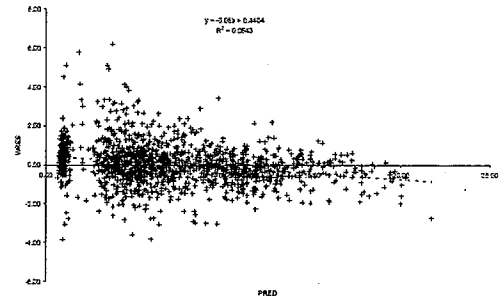


b(4)

Solid line=line of identity (included as a reference)

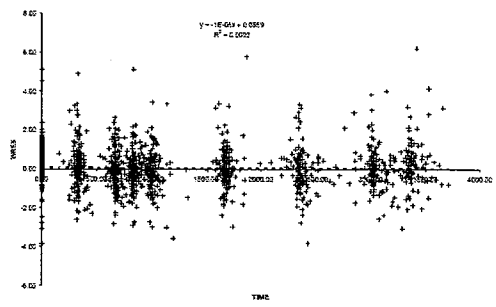
(A)

(B)



Data source: Appendix 6
Dotted line=linear regression (including equation and R^2).

(C)



Data source: Appendix 6
Dotted line=linear regression (including equation and R^2).

(D)

Note: (A) is observed versus population predicted
(B) is observed versus individual predicted
(C) is weighted residual versus population predicted
(D) is weighted residual versus time

5.3.3.2.6 CONCLUSIONS:

LCM plasma concentrations were adequately described by a 1-compartment model with first -order absorption and first-order elimination.

- The mean population PK parameter estimates for k_e and V/f in the target population of subjects with diabetic neuropathy were comparable with those determined in Phase 1 trials in healthy subjects and with those in other population PK analyses. IIV of V/f in the target population (10.1%) was lower compared to the IIV (measured as CV) observed in healthy subjects in Phase 1 trials (20%). The IIV of the rate constant of elimination (k_e) was comparable to the CV observed in Phase 1 trials (IIV of 22.2% in the examined target population compared to CV of 20% in healthy subjects).
- Overall, based on the observed IIV of PK parameters of LCM (IIV=10.1% for V/f, IIV=22.2% for k_e), it can be concluded that LCM plasma concentrations are predictable with good precision in the currently evaluated population.
- According to the criteria specified for covariate selection, body weight and height were identified as the only covariates on V/f among the tested covariates (age, sex, body weight, LBW, height, CL_{cr}, BMI, AST, ALT, GGT, ALK, and total bilirubin). No covariate was found to improve the IIV of k_e.
- The major determinant for V/f was the subjects' height, followed by body weight.

3.2.3.3 Population Pharmacokinetics of Lacosamide in Subjects with Diabetic Neuropathy, Trial Number: SP743

5.3.3.3.1 OBJECTIVES:
The objectives for the population pharmacokinetics of lacosamide from trial SP743 in patients with diabetic neuropathy were:

1. To describe population PK characteristics (i.e., typical mean PK parameters) of LCM and to characterize the inter- and intra-individual variability of the PK parameters of LCM in subjects with diabetic neuropathy.
2. To quantify the relationship between different subject-specific factors (ie, possible covariates, e.g., body weight, creatinine clearance) and PK parameters (apparent volume of distribution [V/f], rate constant of elimination [ke]).

5.3.3.3.2 CLINICAL STUDY OVERVIEW:
The Population PK analyses were performed based on clinical data obtained from trial SP743 in patients with diabetic neuropathy. Detailed information with regard to the study design can be found in section 4.2.2.

A total of 411 subjects were enrolled in this trial. Of the 411 enrolled subjects, 357 (86.9%) were randomized, received at least 1 dose of trial medication, and were included in the Safety Set (SS). Of the 357 subjects in the SS, n=74 were in the placebo group, n=150 in the LCM 400mg/day group, and n=133 in the LCM 600mg/day group.

The first dose of trial medication was taken in the clinic at Visit 2. All subsequent doses of trial medication were planned to be taken in 12-hour intervals, i.e., in the morning and approximately 12 hours following the morning dose (4 tablets in the morning and 4 tablets in the evening).

Lacosamide plasma samples were obtained at all protocol-specified visits following Visit 1, where an electrocardiogram (ECG) was done:
Titration Phase
• Visit 2 (Week 1)
• Visit 3 (Week 3)
• Visit 4 (Week 5)
• Visit 5 (Week 6)
Maintenance Phase
• Visit 6 (Week 7)
• Visit 7 (Week 11)
• Visit 8 (Week 15)
Transition/Taper Phase
• Visit 9 (Week 19)
• Early Termination Visit (for subjects who prematurely discontinued)
Safety Follow-Up
• Termination Visit (for subjects entering the open-label trial)

• Follow-Up Visit (for subjects not entering the open-label trial, or for subjects who prematurely discontinue 14 ± 3 days after the last dose of trial medication)

All plasma samples were obtained at (or near) the same time point as the time of the ECG. At Visit 2, a predose plasma sample was taken at the time of the third ECG and a postdose sample was taken 2 hours after dosing.

5.3.3.3.3 DATA FOR ANALYSIS:
The population PK evaluation was performed based on 1654 concentration records from 264 subjects. The analysis of the plasma samples was performed with a validated high performance liquid chromatography (HPLC) electrospray mass spectrometry (MS) method. The LOQ was 0.05µg/mL for all samples except for the reassayed samples (LOQ of 0.02µg/mL). In the trial SP743, 3063 observations from 358 subjects were recorded. A subset of the plasma concentrations were excluded as described below.

1. The following records were a priori not usable for population PK analysis and had to be excluded from the NONMEM analysis file because concentration records were <LOQ, samples could not be identified, or details on the samples required for analysis were missing (eg, missing sampling/dosing information):
• **Records <LOQ or concentration records relative to LOQ:**
- All 655 records from 74 placebo subjects were excluded.
- 434 records <LOQ from subjects in the verum group were excluded.
- 10 records >LOQ at Visit 2 (predose) before first administration of LCM were excluded, because LCM concentrations were expected to be <LOQ.
• **Concentration records excluded due to missing/inadequate documentation of sampling details:**
- 50 records with missing information on time after administration were excluded.
- 66 records with negative time after administration were excluded.
- 55 records with time after administration >24 hours were excluded.
- 33 records were excluded because the information on the latest dose prior to PK sampling was missing.
- 15 records were excluded because the correct dosing data (with regard to individual morning and evening doses) was not determinable within 3 days prior to PK sampling.

2. The following records were excluded based on the poor dosing compliance of subjects or because the records were considered as outliers:
- 90 records of 16 subjects were excluded because of an overall or daily dosing compliance of <75%.
- 1 record of Subject 13005 with a concentration of 14.344µg/mL was excluded because the measured LCM concentration was 4-fold higher compared to the expected LCM concentration after a single dose of LCM 50mg.

The following parameters were used in the evaluation of possible covariates effect: Age, Sex (Sex=0 for males, Sex=1 for females), Height (HGT), Body weight (BW), Body mass index (BMI), Lean body weight (LBW), Creatinine clearance (CL_{cr}), Aspartate aminotransferase (AST), Alanine aminotransferase (ALT), Gamma glutamyltransferase (GGT), Alkaline phosphatase (ALK), and bilirubin.

Where BMI, CLcr, LBW were calculated by the following formula

$$BMI = \frac{Body\ weight\,[kg]}{(Height[m])^2}$$

$$CL_{cr}\ [mL/\min] = \frac{(140 - age) \times weight\ [kg]}{72 - S_{crea}\ [mg/mL]} \qquad \text{If sex=female then } CL_{cr} = CL_{cr} \times 0.85$$

$$\text{LBW [kg] in males} = 1.10 \times weight[kg] - 0.0128 \times BMI \times weight[kg]$$

$$\text{LBW [kg] in females} = 1.07 \times weight[kg] - 0.0148 \times BMI \times weight[kg]$$

5.3.3.3.4 METHODS:

A one-compartment model with first-order absorption and firs-order elimination (ADVAN2) was used (chosen from prior knowledge) for the population PK evaluation of LCM by using first order conditional estimation method (FOCE) in NONMEM Version IV (NONMEM Project Group, University of California, San Francisco, US)

Model selection was based on a global measure of goodness-of-fit of a model, the objective function (OBF) in NONMEM (= - 2 times the log of the likelihood of the data) was used. In addition, the goodness-of-fit of the different population models for LCM plasma concentrations was assessed by visual inspection of the following diagnostic plots:

- Observed concentrations vs. individual predicted concentrations (DV vs. IPRE)
- Observed concentrations vs. predicted concentrations (DV vs. PRED)
- Weighted residuals vs. predicted concentrations (WRES vs. PRED)
- Residuals vs. predicted concentrations (RES vs. PRED)
- Residuals vs. time (RES vs. time)
- Predicted concentrations and measured concentrations vs. time (PRED/DV vs. time)
- Weighted residuals vs. time (WRES vs. time)
- Individual predicted concentrations and measured concentrations vs. time (IPRE/DV vs. time)

The following criteria were used as additional criteria:

- Reduction of inter- and/or intra-individual (=residual) variability (≥ 1.5%)
- Reduction of the standard errors with respect to parameter estimates
- Analysis of residuals (random and uniform scatter around zero, no time dependency)

The criteria for accepting NONMEM model estimation were the following:

- A "successful minimization" statement by the NONMEM program
- Number of significant digits ≥ 3; if the number of significant digits is <3, reasons for acceptance of the NONMEM run are given.
- Estimates of THETA not close to boundary

Base model evaluation was mainly focus on the selection of residual error model (additive error model, proportional error model, and combined error model) and the inter-individual random effect (additive normally distributed, proportional normally distributed, or log-normal distributed).

Full model was developed to identify possible covariates. The full model was selected by using forward inclusion and backward elimination with the following steps:

- Graphical evaluation of the correlation between individual parameter estimates for k_e and V/f from the base model and potential covariates.
- After the graphical evaluation of the parameter-covariate relationships, each covariate was tested on each of the model parameters k_e and V/f by adding 1 covariate at a time (and removing it) and recording the resulting NONMEM OBF.
- Each of the potential covariates, starting with the "most significant" covariate (=largest OBF difference), was added to the model ("forward inclusion"). If the addition of a potential covariate caused a >7.88-point-decrease of the OBF ($p<0.005$, likelihood ratio test), the covariate was considered as a potentially significant covariate and was added to the model; otherwise, the covariate was dropped from the model.
- In the next step, each potentially significant covariate was removed from the full model individually to determine if a model with fewer parameters would describe the data ("backward stepwise elimination"). If the removal of a potentially significant covariate caused an increase in OBF of at least 10.8 points ($p<0.001$, likelihood ratio test), the covariate was retained in the "final" model; otherwise, the covariate was dropped from the model.

An internal and an external model validation were done with the scope to demonstrate (in addition to the diagnostic plots) that the final model was an adequate description of the data.

- **Internal Model Validation**
  After building the final model, an internal model validation was done using the method of data splitting of the corresponding analysis file with the concentration data included in the NONMEM analysis. The final model (run 038) was applied to each of the datasets and the results of these two runs were compared with the results of the final model using the NONMEM analysis file with the concentration data of all subjects

- **External Model Validation**
  An external model validation was done by showing that the applied model in the current evaluation (1-compartment-model, ADVAN2) provides a good prediction of LCM concentration data obtained during full sampling in 2 Phase 1 trials in healthy subjects.

5.3.3.3.5 RESULTS:

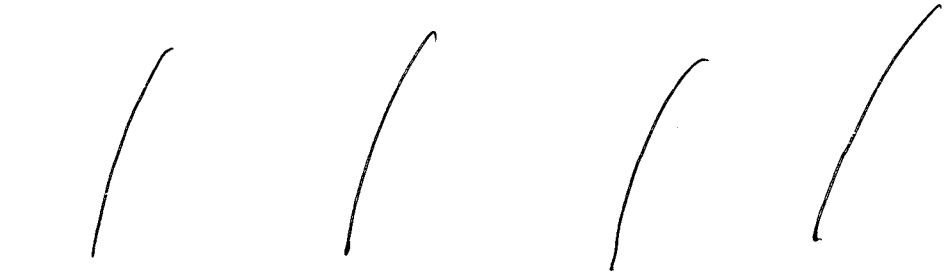
The structure model for the base model was one-compartment model with first-order absorption and first-order elimination, including log-normally distributed inter-individual variability on Ke and V/f. Ka was fixed to 4.0. The residual was described as a proportional error model. The model parameter estimates were summarized in Table 15 and the major goodness-of-fit plots were shown in Figure 17 .

Table 15 Lacosamide Base Population PK Model Parameter Estimates Derived from Trial SP 743

Parameter	Final estimate	RSE [%]
k_e [h^{-1}][a]	0.0372	2.82
V/f [L]	43.2	2.11
k_a [h^{-1}]	4.00	n.d.
Parameter	**IIV [%]**	**RSE [%]**
k_e [h^{-1}]	26.5	19.5
V/f [L]	18.8	24.3
k_a [h^{-1}]	n.d.	n.d.
Residual error	**Final estimate**	**RSE [%]**
Proportional	26.6%	8.66

RSE[%]= percent relative standard error of the estimate or variance estimate for IIV; IIV[%]=Inter-individual variability in percent; n.d.=not determined
a k_e of 0.0372h^{-1} corresponds to a $t_{1/2}$ of 18.6h
Data source: Appendix 3, Appendix 7

Figure 17 Goodness-of-fit for Lacosamide Base Population PK Model Derived from Trial SP 743



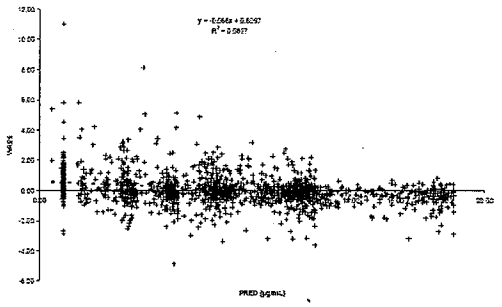
Solid line=line of identity (included as a reference)
Data source: Appendix 6

(A)

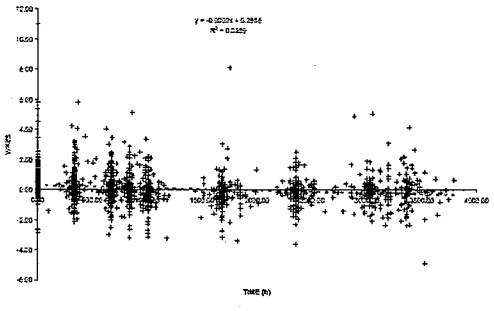
Solid line=line of identity (included as a reference)
Data source: Appendix 6

(B)

b(4)



(C)



(D)

Note: (A) is observed versus population predicted
(B) is observed versus individual predicted
(C) is weighted residual versus population predicted
(D) is weighted residual versus time

The final model was selected from the base model chosen with the same inter-individual variability structure and the same error structure. The covariate effect and parameter estimates were summarized in Table 16. Goodness-of-fit plots were shown in Figure 18.

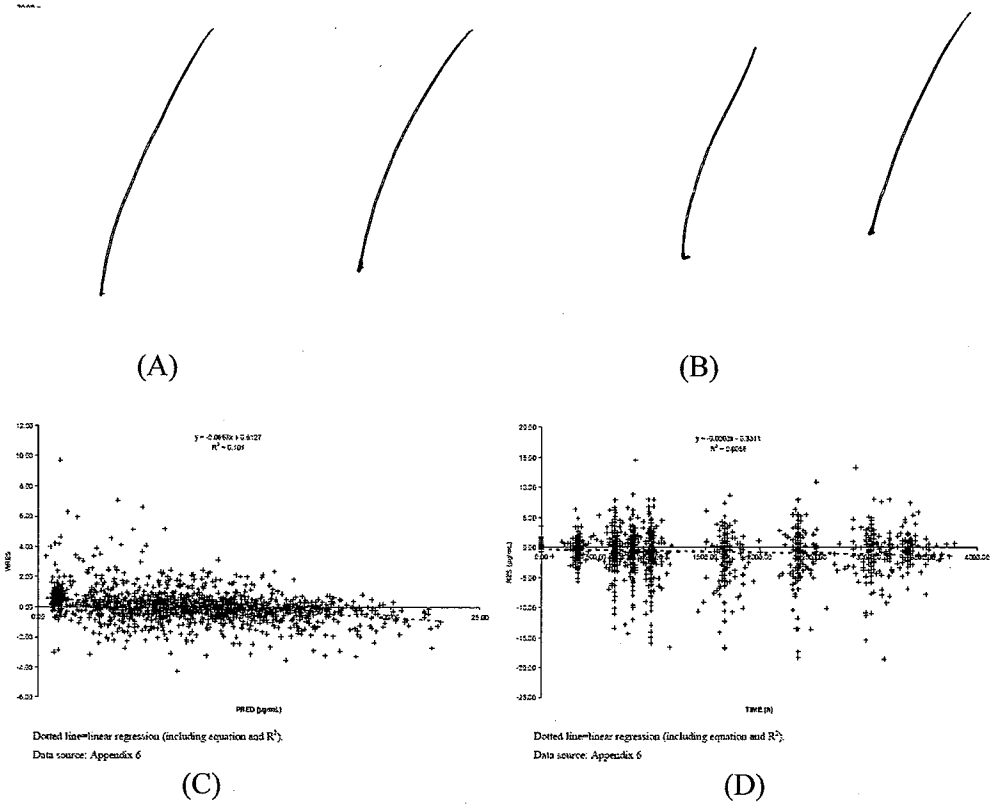
Table 16 Lacosamide Final Population PK Model Parameter Estimates Derived from Trial SP 743

Parameter	Final estimate	RSE [%]
k_a [h^{-1}]	$k_a = \theta 1$	n.d.
θ1	4.00 (fixed parameter)	n.d
k_e [h^{-1}]	$k_e = \theta 3 + \theta 5 \times (Age - 57.8)$	n.d.
θ3	0.0364	2.80
θ5	-0.000280	29.3
V/f [L]	$V/f = \theta 2 + \theta 4 \times (LBW - 57.7)$	n.d.
θ2	44.2	1.86
θ4	0.717	10.9
Parameter	**IIV [%]**	**RSE [%]**
k_e [h^{-1}]	27.6	20.8
V/f [L]	15.8	33.4
Residual error	**Final estimate**	**RSE [%]**
Proportional	25.0%	8.44

RSE[%]=percent relative standard error of the estimate or variance estimate for IIV; IIV[%]=Inter-individual variability in percent; LBW=lean body weight; θ1=typical value of k_a; θ2=typical value of V/f without effect of covariate; θ3=typical value of k_e without effect of covariate; θ4=slope of the effect of covariate LBW on V/f; θ5=slope of the effect of covariate age on k_e
Data source: Appendix 3, Appendix 7

Figure 18 Goodness-of-fit for Lacosamide Final Population PK Model Derived from Trial SP 743

b(4)



Note: (A) is observed versus population predicted
(B) is observed versus individual predicted
(C) is weighted residual versus population predicted
(D) is weighted residual versus time

The sponsor performed both internal and external model validations. For internal model validation, the population PK dataset was randomly split into two subsets and used for population PK model validation. The validation was preformed by re-analyzing overall dataset and the two subsets using the final model. The results showed that the population PK parameter estimates and the residual variability were comparable for both sub-datasets and comparable with the results form analyzing the complete dataset with all subjects. For external model validation, the sponsor indicated the appropriateness of the applied one-compartment model that was used in the current evaluation of the dscription of SP743 LCM concentration data. In addition, the findings for V/f in the current evaluation were in agreement with the SP640 Popoulation PK results, where V/f was best predicted based on LBW and height of subjects.

5.3.3.3.6 CONCLUSIONS:

Lacosamide plasma concentrations were adequately described by a 1-compartment model with first-order absorption and first-order elimination (ADVAN2).

- Overall, the mean population PK parameter estimates for ke and V/f in the target population of subjects with diabetic neuropathy were comparable with those determined in Phase 1 trials in healthy subjects. The low IIV of V/f in the target population (IIV=15.8%) was determined to be comparable with the IIV observed in healthy subjects in Phase 1 trials (CV=20%). The IIV of V/f was a priori low, even without inclusion of covariates (IIV=18.8%, base model without covariates). The IIV of the rate constant of elimination (ke) was slightly higher compared to the CV observed in Phase 1 trials (IIV of 27.6% in the examined target population compared to CV of 20% in healthy subjects).
- Overall, based on the observed low IIV of PK parameters of LCM (IIV=15.8% for V/f, IIV=27.6% for ke), it can be concluded that LCM plasma concentrations are predictable with good precision in the currently evaluated target population.
- According to the criteria specified for covariate selection, LBW was identified as a covariate on V/f and age was identified as a covariate on ke.
- Based on the final model results, the major determinant for V/f was the subjects' LBW. This means that V/f and therefore LCM plasma concentrations can be best predicted based on subjects' LBW.
- Based on the final model results, elimination of LCM is influenced by age, as a slightly prolonged $t_{1/2}$ of LCM is observed with increasing age.

3.3 INDIVIDUAL EXPOSURE-RESPONSE ANALYSES REPORTS

The sponsor submitted two exposure-response analyses reports with regard to the two indications of lacosamide, including report SPM927 (pharmacokinetic-pharmacodynamic modeling of lacosamide in subjects with partial-onset seizures) and report SPM929 (pharmacokinetic-pharmacodynamic modeling of lacosamide in subjects with painful distal diabetic neuropathy). The two reports were summarized as following:

3.3.1 Report SPM927:

The pharmacokinetic-pharmcodynamic (PK-PD) analysis of lacosamide in subjects with partial onset seizures based on data collected from trials SP667, SP754, and SP755 was described in study report SPM927..

3.3.1.1 Objectives

Objectives of the PK-PD analysis were to evaluate and describe the correlation between the LCM plasma concentration over time (PK parameter) and the reduction of daily seizures over time (PD parameter) based on the pooled data from the trials SP667, SP754, and SP755 that comprise Pool E1 as defined in the Integrated Summary of Efficacy (ISE).

The results of this PK-PD modeling should provide supportive information about the therapeutic LCM dose range.

3.3.1.2 Study Overviews

The PK-PD analyses were performed based on clinical data obtained from trial SP667, SP754, and SP755. Detailed information with regard to the study design can be found in section 4.2.1.

3.3.1.3 Data for analyses

Subjects included in the PK-PD analysis:

In total, there were 9707 records available. For creation of the PK-PD modeling input file, the following records were excluded:

1. 3098 records from placebo subjects
2. 1611 records with concentrations below the lower limit of quantification
3. 36 records with negative sampling times
4. 47 records with a time after administration of >24 hours
5. 11 records with measurable LCM concentrations before the first administration of trial medication
6. 1849 records were excluded because subjects were ineligible to enter the analysis as no evaluable slope for the Baseline Phase could be derived, or R^2 for the slope at Baseline Phase was determined to be <0.95 (both indicates nonresponders).

Finally, 3055 records from 615 subjects were evaluable for the PK-PD analysis and are part of the input file for the PK-PD analysis.

Exposure Variable:
The PK parameter of interest in the current PK-PD evaluation is the individual LCM exposure, quantified by the area under the LCM plasma concentration-time curve within a dose interval of 12 hours under steady-state conditions (AUCτ,ss). The sponsor generated the steady state AUC over a dosing interval.

Response Variable:
The daily number of partial seizures for each subject at each dose step, at Baseline, during Titration, and during Maintenance Phase have been evaluated and was chosen as the PD variable.

The integral of the daily number of seizures over time is equal to the cumulative number of seizures over time (and this equates to the total number of seizures).

$$N = \sum_{i=1}^{k} n_i$$

K = number of days under a dose level, ni = daily number of seizures, and N is the cumulative daily number of seizure.

For the PK-PD modeling, the PD parameter 'daily number of seizures' was used to find the mean daily number of seizures within a time interval at a fixed dose. The linear regression of the cumulative daily number of seizures results in the slope and the intercept for each dose level. The slope is equal to the mean daily number of seizures in the time interval of regression.

3.3.1.4 Methods

The PK-PD analysis was conducted using the SAS® procedure *proc nlin* with the Marquardt iteration algorithm (SAS® Package version 8.2, SAS Institute GmbH, Heidelberg, Germany). The following three models were tested:

- Linear model
- E_{max} model

$$E(AUC) = E_{max} \cdot \frac{AUC_{\tau,SS}}{AUC_{50} + AUC_{\tau,SS}}$$

- E_{max} 100 model

$$E(AUC) = 100 \cdot \frac{AUC_{\tau,SS}}{AUC_{50} + AUC_{\tau,SS}}$$

3.3.1.5 Results

Based on the goodness-of-fit tests, the Emax model was identified as the most adequate model. For the E_{max} model evaluation, data across the Baseline, Titration, and

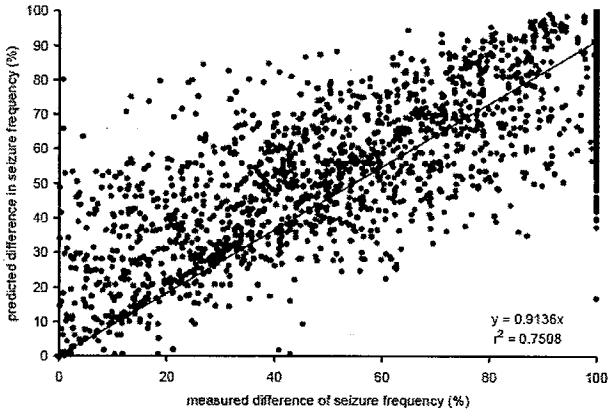
Maintenance Phases were used. The following table (Table 17) summarizes the PK-PD modeling results using the Emax model.

Table 17 PK/PD Results based on Emax Model (N=615 Subjects)

Parameter	Arithmetic mean (SD)	Median	Range	1st, 3rd quantile
AUC50[a] [µg/mL*h]	35.9 (185.6)	1.05	0-3998	0, 27.27
E_{max} [%]	71.0 (30.0)	77.0	0.06-100	47,7,100

a AUC50=AUC needed to achieve half of the maximum effect
Data source: Appendix 9 (Part 2)

Figure 19 Diagnostic Plots for the Model Results



3.3.1.6 Conclusions

All tested PK-PD models (linear model, Emax model, Emax 100 model) resulted in model parameter results with very high variability. The Emax model showed the lowest weighted sum of squares and was therefore identified as the most appropriate PK-PD model to describe the relation between AUC and seizure frequency change.

- As a result of the Emax model, the AUC_{50} (i.e., $AUC_{\tau,ss}$ to achieve 35% decrease in partial seizure frequency corresponding to a decrease of 50% of the maximum effect) was estimated to be 35.9µg/mL×h. This $AUC_{\tau,ss}$ corresponds to an $AUC_{\tau,ss}$ that is obtained in individuals by administration of a dose of about 110mg LCM bid in a typical subject with a volume of distribution of 50L and a k_e of 0.06h^{-1} (corresponding to a terminal half-life of approximately 12 hours).
- Based on the current results of the Emax model, it can be predicted that an $AUC_{\tau,ss}$ of 67µg/mL×h (corresponding to a mean dose of 200mg bid in a typical subject)

is needed to have a decrease of the daily number of seizures of 46% corresponding to a decrease of 65% of the maximum effect, whereas an $AUC_{\tau,ss}$ of 100µg/mL×h (corresponding to a mean dose of 300mg LCM bid in a typical subject) is needed to have a decrease of the daily number of partial seizures of 52% corresponding to a decrease of 74% of the maximum effect. b(4)

- The current PK-PD results support the therapeutic range of LCM doses (200-— mg/day) that have been shown to be effective as an adjunctive treatment for reducing partial seizure frequency.

REVIEWER'S COMMENTS ON SPONSOR ANALYSIS

1. The sponsor performed exposure-response analysis in patients with partial seizure and in patients with painful distal diabetic neuropathy.

1.) In the study report, we found that the sponsor applied two-stage analysis by firstly estimating PD parameters for each individual and then obtaining the population parameters. It is acceptable. Nevertheless, in order to reduce bias in parameter estimates, we recommend that the sponsor apply mixed effect model to estimate fixed effect and random effect simultaneously.

2.) Current modeling approach is mainly focused on the responder patient population (Non-responder and placebo group patients were excluded). Whether to use all patients or responders in exposure-response analysis serves different roles. For understanding the effectiveness of the drug, all patients must be used in the analysis. For justifying the selection of optimal dose, responder analysis represents a better approach. However, the non-responder should be analyzed separately to learn if higher doses or some baseline characteristics can aid in improving response.

3.) Likert Pain Score and Change from Baseline of Average Daily Number of Seizures are affected by both lacosamide exposure and time. The analyses conducted by the sponsor only focused on the relationship between response variables and exposure, ignoring time effect. We recommend that the sponsor incorporate the time effect in the modeling using longitudinal data.

2. The sponsor performed population PK analysis in healthy subjects and patients with partial seizure and distal diabetic neuropathy.

1.) The sponsor fixed Ka in the population PK analysis. Especially, different values of Ka were chosen in different patient population in different reports. It is acceptable that the sponsor fixed some of the parameters in the analysis. However, the sponsor should provide adequate rationale.

2.) In the graphics-based selection of covariates, the sponsor plotted the individual parameters versus different covariates. We recommend that the sponsor use the interindividual variability (referred to as ETAs in NONMEM jargon) of different PK parameters derived from the final base model (i.e., without the covariates in question) rather than using the parameter estimates by themselves.

4 REVIEWER'S ANALYSIS

FDA reviewer's analysis was to explore the exposure-effectiveness relationship following Lacosamide therapy.

4.1 EXPOSURE-RESPONSE RELATIONSHIP IN PATIENTS WITH PARTIAL-ONSET SEIZURES

Our analyses were performed to investigate the exposure-response relationship in patients with partial onset seizures.

4.1.1 Dataset

The reviewer's analyses dataset (variable: from_al2 equals = 1) was based on the sponsor's analyses dataset (pkpd.xpt) used in study report SPM 927 (Pharmacokinetic-pharmcodynamic modeling of lacosamide in subjects with partial-onset seizures). The description of the dataset is detailed in Section 5.4.1.3. It is to note that only responders were included in the dataset, with non-responder and placebo treated patients being excluded. Unlike the sponsor's analyses, in which the observation across various time points in the trial were pooled together, our analyses were focus on two critical time points, i.e. by the end of the titration phase and by the end of the maintenance phase. The observations under different time points were listed in Table 19. It is to note that if there were multiple observations for the same individual in the selected time window, the first observation was used in the analyses.

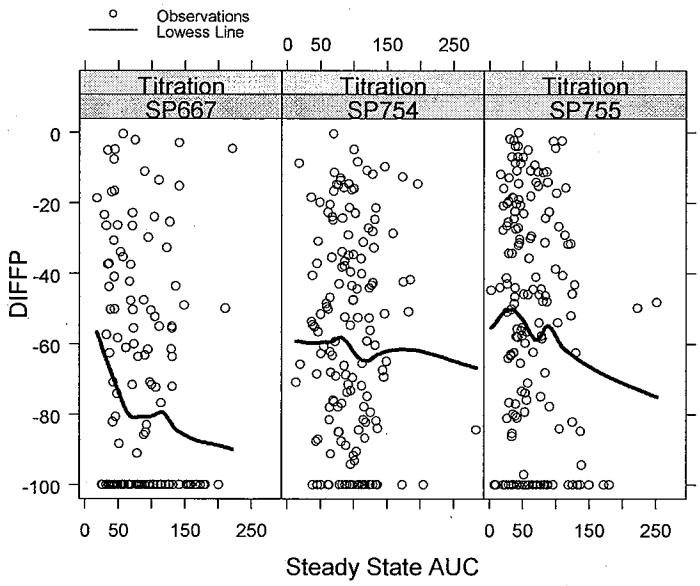
Table 19 Summary of Observations at Two Different Time Points

	End of Titration Phase			End of Maintenance Phase		
Study	Planned	Criteria #1	Included #2	Planned	Criteria #1	Included #2
SP-667	6 weeks	Day 42±3	147 Obs / 147 Sub	12 weeks	Day 126±5	132 Obs / 132 Sub
SP-754	6 weeks	Day 42	161 Obs / 161 Sub	12 weeks	Day 126	122 Obs / 122 Sub
SP-755	4 weeks	Day 28 ±3	170 Obs / 170 Sub	12 weeks	Day 117±5	167 Obs / 167 Sub

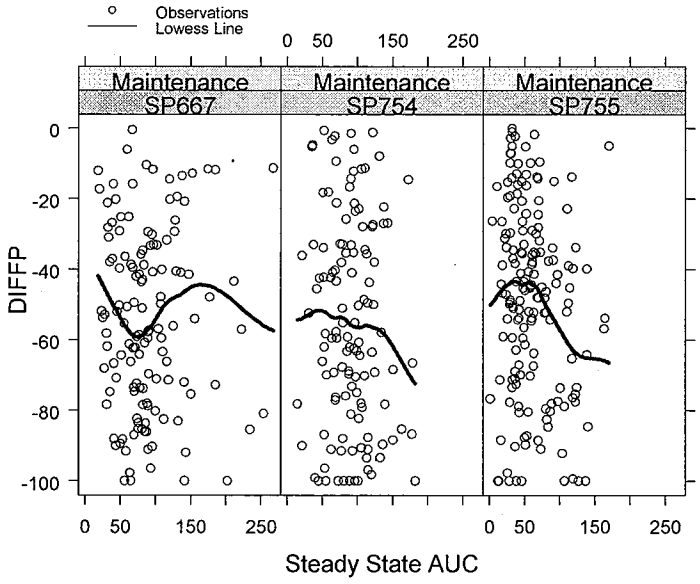
#1: Observations within the criteria window were included in the analyses (based on variable DAY_TOT)
#2: One observation (Obs) per subject (Sub)

A preview of the observations by the end of titration phase and maintenance phase indicated that there is an exposure-response association. Higher exposure (expressed as steady state AUC) is related with larger changes in the average daily number of partial seizures from baseline (DIFFP).

Figure 22 Preview of Change in Average Daily Number of Partial Seizures (DIFFP) and Exposure (Steady State AUC) by Study and Different Observation Phase (End of Titration Phase and End of Maintenance Phase)



(A)



(B)

Note: (A) represents the observations by the end of titration phase.
(B) represents the observations by the end of maintenance phase.

4.1.2 Exposure-Response Analyses

The exposure-response relationship was demonstrated both by the end of titration phase and by the end of maintenance phase. Based on the exposure-response relationship, 400 mg dose yields similar outcome as compared to 600 mg dose.

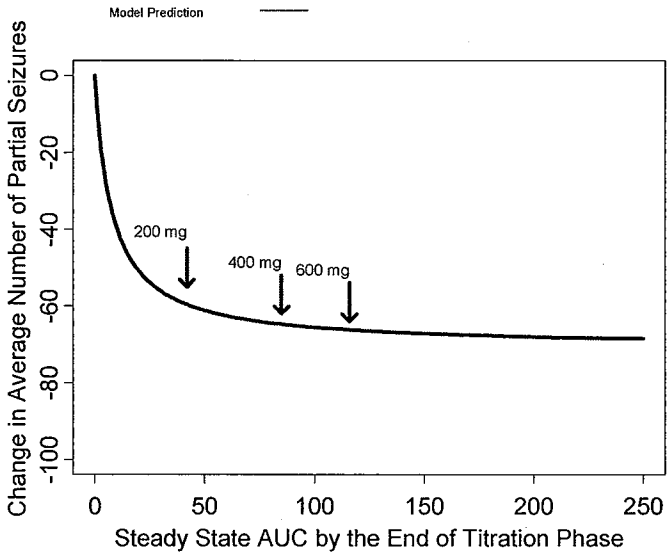
The analyses were performed by using observations from the three clinical trials (SP667, SP754, and SP755). Each observation was from different individual. Hence, they were assumed to be independently and identically distributed. The error term is assumed to follow Gaussian distribution. Emax model was used to describe the relationship between steady state AUC (exposure) and change from baseline in average daily number of partial seizures (DIFFP). Nonlinear least square method by using nls and nlsList function in S_Plus (S_Plus 7.0 for windows, Professional developer, Insightful Corp) or PROC NLIN in SAS (SAS 9.1 level 1M3, SAS Inc) was applied. It is to note that placebo group and non-responder patients were excluded from the analysis dataset, the curve beyond the observation range might not be accurate.

Significant exposure-response relationship was identified by the end of titration phase and by the end of maintenance phase ($P < 0.0001$). The results from the end of titration phase and from the end of maintenance phase were presented in Table 20. Based on the established exposure-response relationship, the mean response from 400 mg dose is similar to 600 mg dose (Figure 23).

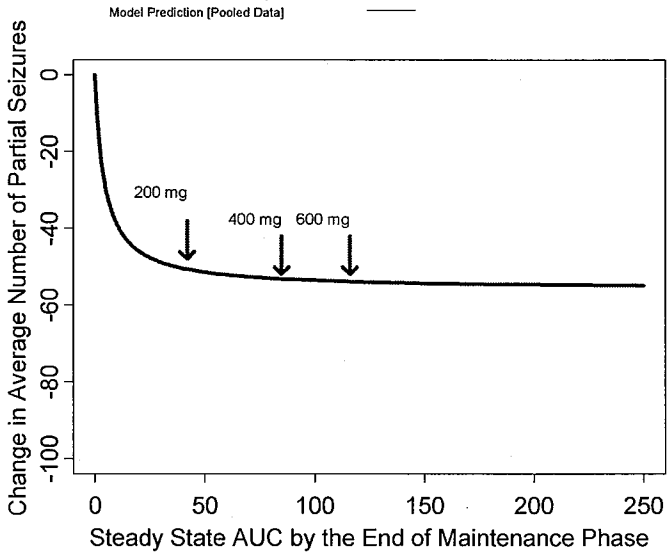
Table 20 Summary of the Nonlinear Least Square Model Using Observations by the End of Titration Phase

		Parameter Estimate		
		Emax	EC 50	Significance of Model Parameters
Titration Phase	Pooled Data	-70.7	7.8	< 0.0001
Maintenance Phase	Pooled Data	-55.9	4.3	< 0.0001

Figure 23 Model Predicted Response at the End of Titration Phase (A) and at the End of Maintenance Phase (B)



(A)



(B)

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✓ Trade Secret / Confidential (b4)

_____ Draft Labeling (b4)

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Hao Zhu
6/4/2008 03:21:26 PM
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Jogarao Gobburu
6/5/2008 02:15:24 PM
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BIOPHARMACEUTICS REVIEW

b(4)

NDA and Submission numbers	**NDA 022-253, 022-254,**
Drug name, drug substances, dosage form and strength	**Lacosamide 50-, 100-, 150-, 200- and 300-mg film-coated tablets**
Submission date	**September 28, 2007**
Sponsor	**Schwarz Biosciences**
Clinical Divisions	**Division of Neurology Products and Division of Anesthesia, Analgesia and Rheumatology Products**
Primary CMC Reviewer	**Prafull Shiromani, Ph.D.**
Biopharmaceutics Reviewer	**Arzu Selen, Ph.D.**

b(4)

EXECUTIVE SUMMARY AND RECOMMENDATION

Lacosamide is a new chemical entity , (R)-2-acetamido-N-benzyl-3-methoxypropionamide). It was also called harkoseride, ADD 23-4037 and SPM927, and is claimed to have anti-epileptic and analgesic activity in preclinical models and clinical trials, although, the precise mechanism of action of lacosamide, as an anti-epileptic and analgesic is not fully elucidated.

b(4)

In the NDA, based on its elimination half-life (approximately, 11 hrs), and its assessment in the clinical trials, the Sponsor proposes daily doses of 200- mg lacosamide administered in two equally divided doses. (At the time of this review, the clinical assessments are ongoing.)

b(4)

There are related NDA submissions under review: as an adjunctive therapy in the treatment of partial-onset seizures in patients with epilepsy aged 16 years and older (NDA 022-253, 022-254 for dosage forms: tablet, solution for iv infusion, and for the management of neuropathic pain associated with diabetic peripheral neuropathy (NDA The NDA 022-253 serves as the primary NDA to which the other NDAs refer to, as applicable.

b(4)

Of the several dosage forms of lacosamide, the solid oral lacosamide drug product for the treatment of epilepsy and neuropathic pain is an immediate release film-coated tablet: 50 mg (pink), 100 mg (dark yellow), 150 mg (salmon), 200 mg (blue), 250 mg and 300 mg and the solution for infusion contains 10 mg/mL lacosamide. The iv infusion is intended for use in patients with epilepsy when oral administration, temporarily, is not feasible.

b(4)

This biopharmaceutics review specifically addresses the following:

a) *in vitro* dissolution and product characteristics (related *in vivo* considerations)
b) the biowaiver requests for the proposed commercial tablets

b(4)

The Sponsor has shown in multiple media that lacosamide tablets are highly soluble (pH range 1 to 7.5) and based on the submitted data, the following dissolution method for the lacosamide tablets is acceptable:

USP Apparatus 2 (Paddle)
Test medium: 0.1 N HCl, 900 mL
Temperature: 37° C ± 0.5°C
Paddle rotation speed: 50 rpm
Q= at 30 min

b(4)

For the CMC review including complete product quality assessment and specification for the lacosamide dosage forms, please see Dr. Prafull Shiromani's review.

In the NDA, although lacosamide dissolution testing was carried out at 50 rpm paddle rotation speed, the Sponsor proposes — rpm for the dissolution specification, however, consistent with the submission, the Sponsor should maintain the original paddle speed of 50 rpm for dissolution testing.

During early development, in clinical trials, lacosamide capsules were used in some of the phase 1 and early phase 2 trials. Subsequently, a tablet formulation with 50 mg or 100 mg lacosamide has been used and — ne proposed commercial tablet with dosages up to 300 mg was developed. The manufacturing process for both the clinical trial formulation and the proposed commercial tablet formulation includes — The composition of the proposed commercial tablets is different from that of the clinical trial tablets, and the same — s used for the various strengths of the proposed commercial tablets. b(4)

The proposed commercial tablets have not been studied *in vivo* and hence, the Sponsor is requesting a biowaiver for the proposed commercial tablets (50-mg t — mg strengths). The Sponsor refers to past discussions with FDA where they obtained an agreement from the Agency that further *in vivo* bioequivalence assessments would not be needed for the proposed commercial tablets (which are considered to behave similarly to the clinical trial tablets, *in vivo*). Note: At the 11/3/2004 meeting for IND 57,939 (i.e. SPM 927 or lacosamide tablets), the Sponsor was told that need to verify that BCS 1 classification is applicable, otherwise, because the formulation of the proposed commercial tablets are different than those studied in the clinical trials, they will need to conduct a bioequivalence study to demonstrate that they are bioequivalent. b(4)

The Sponsor has submitted adequate information to support classification of lacosamide tablets according to the Biopharmaceutics Classification System (BCS) as a BCS class 1 drug. That is, the drug substance is highly soluble, highly permeable and the tablets are rapidly dissolving as demonstrated by the following:

1) High solubility: The highest strength is soluble in <250 mL over the pH range of 1-7.5.
   At the five tested dissolution media (pH 1.0, 3.0, 4.5, 6.5 and 7.5), the lowest solubility of lacosamide was — mg/mL at pH 7.5 in the phosphate buffer. This translates into requiring — mL of the pH 7.5 phosphate buffer to dissolve the highest strength (300-mg) lacosamide film-coated tablets. b(4)
2) High permeability: 90% or more of the oral dose is absorbed.
   Following oral administration of ^{14}C-radiolabeled 100-mg dose of lacosamide (solution), 94% of the administered dose was recovered in urine (Study SP619) and in other studies (SP658 and S645), lacosamide exposure was identical following oral and iv administration, indicating 100% absolute bioavailability.
3) Rapidly dissolving: Multiple strengths of the lacosamide tablets were tested in the three pH media (pH 1.0, 4.5 and 6.8), and 85% or more of lacosamide was dissolved in 15 min.

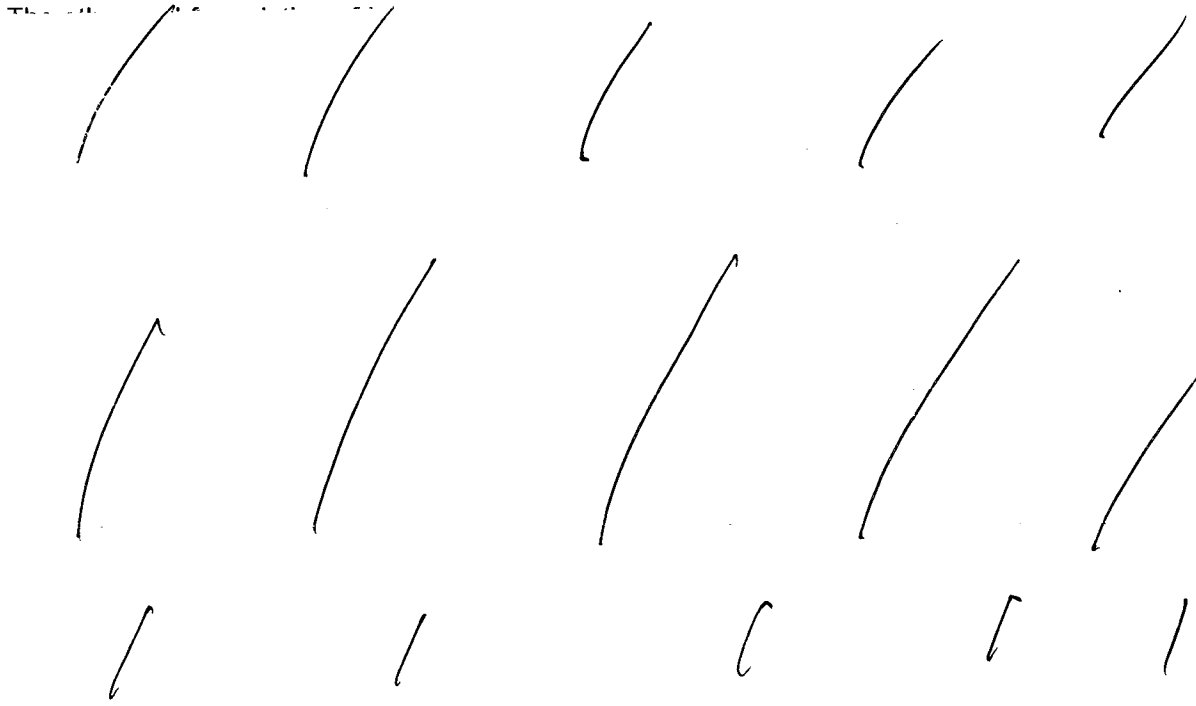
As a result, *in vitro* bioequivalence assessments are considered acceptable for lacosamide tablets per the BCS guidance (Guidance for industry: Waiver of *in vivo* bioavailability and bioequivalence studies for immediate-release solid oral dosage forms based on a biopharmaceutics classification system, 2000).
In addition, although differences are noted in the composition of the proposed commercial tablets and the clinical trial tablets, the excipients included in the proposed commercial tablets are well characterized and can not further increase the lacosamide bioavailability (i.e. lead to unexpected lacosamide exposures) as the absolute lacosamide bioavailability from the clinical tablets is 100%.

The submitted *in vitro* dissolution data (multiple sample collection time points, and multiple media) also show that the excipients would not have an unfavorable effect on vivo performance of the tablets, as both products have similar *in vitro* dissolution rates, rapidly dissolve within 15 min, and being a BCS 1 class drug, lacosamide once in solution, should be equally rapidly absorbed from both formulations (clinical trial tablets and the proposed commercial tablets).

Another consideration has been the difference in the strengths of the clinical trial tablets (50-mg and 100-mg) and the proposed commercial tablets (50-mg to 300-mg). Given that both tablets should behave similarly *in vivo*, and all strengths of the proposed commercial tablets are compositionally-proportional and that lacosamide pharmacokinetics are linear (per Dr. Emanuel Fadiran's clinical pharmacology review), the extension of the biowaiver to the 300-mg strength lacosamide tablets can be justified without requiring further *in vivo* studies. This approach is consistent with the Bioavailability Guidance (Guidance for Industry, Bioavailability and Bioequivalence Studies for Orally Administered Drug Products — General Considerations, 2003) as the linearity of the drug pharmacokinetics is established over the dose range under consideration, and the clinical studies were conducted up to and including 800 mg daily doses (as 400 mg bid) of lacosamide for extended periods ensuring that the lacosamide exposures from the proposed commercial tablets are within the clinically studied exposure range.

b(4)

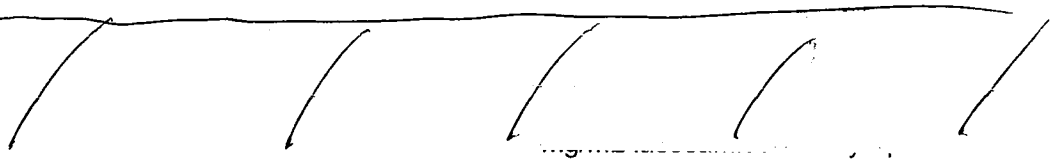
Dr. Prafull Shiromani's comprehensive review of the data submitted in support of the biowaiver request is incorporated into this review (into Section 2 of the main text) with information on product composition and comparisons (Appendix A), and *in vitro* dissolution data in the three media (Appendix B).



b(4)

May be communicated to the Sponsor

In vitro and *in vivo* performance of the lacosamide clinical trial tablets are adequately characterized and the information gained from the clinical trial tablets can be extrapolated to the proposed commercial tablets.



b(4)

Recommendation:

b(4)

The Sponsor has provided adequate *in vitro* and *in vivo* characterization of the various lacosamide formulations, and adequate data to support their biowaiver requests for the *in vivo* assessment of the lacosamide proposed commercial tablets (50-mg, 100-mg, 150-mg, 200-mg,

The proposed dissolution method and their biowaiver requests are acceptable.

Signature:

Arzu Selen, Ph.D.
Associate Director, Biopharmaceutics
Office of New Drug Quality Assessment

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Review of the related *in vitro* and *in vivo* studies

Table of Contents

b(4)

b(4)

1. Background

The following NDAs are submitted for lacosamide:

1) NDA 22-253; Lacosamide (SPM 927) Tablets
For the treatment of Epilepsy as adjunctive therapy in patients with partial onset seizures aged 16 years and older
2) NDA 22-254; Lacosamide (SPM 927) Injection
For the treatment of Epilepsy as adjunctive therapy in patients with partial onset seizures aged 16 years and older when oral administration is temporarily not feasible

b(4)

The early clinical trial program for lacosamide is stated to have started with hand-filled hard gelatin capsules, filled with 50-mg, 100-mg, or 200-mg of the pure drug substance. Subsequently, in the course of development, capsules were filled with a powder blend of lacosamide and excipients. b(4)

, SCHWARZ Biosciences developed an immediate-release film-coated tablet containing 25-mg, 50-mg, or 100-mg lacosamide to be used in clinical trials. The 25-mg dose strength was only used in trials in subjects with diabetic neuropathic pain. The lacosamide tablet was used in the majority of clinical trials from Phase 1 through Phase 2/3 and in addition, a solution for infusion were also developed as alternative drug formulations to the tablet. Lacosamide dosage forms used/studied in the clinical trials are listed in Appendix D.

Currently, there are two manufacturing sites for the proposed commercial tablets: SCHWARZ PHARMA Produktions-GmbH, Zwickau, Germany and SCHWARZ PHARMA Manufacturing Inc., Seymour, Indiana, USA.

The composition of the proposed commercial tablet is slightly different from the tablet used in clinical development (please see Appendix A). Both formulations are immediate-release film-coated tablets which differ in size, shape, color, and composition, and the Sponsor claims that the difference in composition between the two tablet formulations is "minor". This reviewer does not consider the difference between the two formulations to be "minor", however, based on BCS 1 classification of lacosamide and that the tablets are rapidly dissolving, agrees that the net effect of the difference should be negligible *in vivo*.

b(4)

2. Assessment of the data submitted for the biowaiver request (for the proposed commercial tablets)

Lacosamide tablets are immediate-release, oral, film-coated tablets manufactured by a conventional The formulation used in clinical trials b(4)
is a tablet, identical in size to allow for blinding. An additional 25 mg dosage strength was used in only single phase 2 study one study (SP655). The tablets for commercial supply contain 50, 150, 200, mg of drug substance. They are immediate-release, oval, film-coated tablets of different size and mass and are **compositionally proportional**

. The primary stability batches were coated with a film-coat whereas the commercial product will be coated with different colors for the individual strengths. The dissolution characteristics were observed to be very similar between the clinical and commercial formulations. The commercial tablet formulation and the comparison between this formulation and the clinical tablet formulation is given in Appendix A. Composition for the capsule formulations is also given in the same Appendix.

b(4)

Immediate release capsule formulations were used in initial clinical trials; initially, the DS (50, 100, or 200 mg) manually filled into hard gelatin capsules and later machine filled capsules containing a blend of lacosamide, and magnesium stearate.

b(4)

A waiver of *in vivo* bioequivalence studies for the commercial formulation is requested.

2.a. *in vitro* dissolution of formulations used in clinical trials and the proposed commercial tablet

A. Comparison of *in vitro* dissolution of immediate-release capsules with pure lacosamide and a blend of lacosamide with excipients as well as 50 mg and 100 mg film-coated tablets used in clinical trials is presented in the table below:

b(4)

In vitro dissolution of solid oral dosage forms of lacosamide (capsules and tablet)

Formulation	Capsule filled with pure drug substance	Capsule filled with powder blend	Tablet	
Strength:	100 mg	100 mg	50 mg	100 mg
Batch no.:	33548 mean, n=6	54997 mean, n=6	20012022 mean, n=6	215330 mean, n=6
Drug dissolved [%]				
10 min	88	94	89	94
20 min	99	101	96	98
30 min	101	102	99	100

Method: Paddle apparatus, 900 mL 0.1 N HCl, 37 ± 0.5°C, 50 revolutions per minute

Evaluation

Both capsule formulations as well as the tablets are characterized by similar rapid dissolution *in vitro*.

B. *In vitro* dissolution of 100 mg tablets used in bioavailability bioequivalence trials

The 100 mg tablet was used in the bioavailability and bioequivalence trials (SP600: Effect of food on the bioavailability of lacosamide; SP645 and SP658: Comparison of pharmacokinetics and lacosamide when given as oral tablet or as intravenous solution; . The dissolution data is shown below:

b(4)

Dissolution of 100 mg tablets – bioavailability/bioequivalence trials

Time	Mean [%]	Range [%]	RSD [%]
Batch no. 215330 used in SP600 (n = 6)			
15 minutes	100	93 - 106	4.6
30 minutes	100	100 - 102	0.8
Batch no. 223770 used in SP645 (n = 12)			
15 minutes	96	89 - 100	3.2
30 minutes	98	92 - 101	2.4
Batch no. 228920 used in SP658 (n = 6)			
15 minutes	98	93 - 101	2.9
30 minutes	100	95 - 101	2.2
Batch no. 231120 used in SP657 (n = 6)			
15 minutes	96	93 - 100	3.0
30 minutes	97	94 - 100	2.4

Method: Paddle apparatus, 900 mL 0.1 N HCl, 37 ± 0.5°C, 50 revolutions per minute

Evaluation

The dissolution data for the batches show that the dissolution characteristics of the tablet were consistent across batches. In all batches, rapid dissolution occurred with >85% of the DS being dissolved at 15 minutes.

C. Comparison of *in vitro* dissolution of immediate-release commercial formulation and tablet formulation used in clinical trials to justify a biowaiver request.

C.1 The proposed commercial tablet formulation with — film-coat

The sponsor states that according to current guidance documents (FDA: Guidance of Industry, Waiver of *In Vivo* Bioavailability and Bioequivalence Studies for Immediate-Release Oral Dosage Forms Based on a Biopharmaceutics Classification System, 2000 and CPMP: Note for Guidance on the Investigation of Bioavailability and Bioequivalence, 2001), an exemption from *in vivo* bioequivalence studies for oral immediate-release tablets can be justified if the DS is categorized as Class 1 (high solubility and high permeability of the DS) and high dissolution rate for the product. The sponsor presents the following data to support these characteristics.

Data supporting high solubility:

According to the BCS, a drug substance is considered highly soluble when the highest dosage strength is soluble in </= 250 mL of aqueous media over a pH range of 1 to 7.5. The sponsor has presented the data to confirm the high solubility of the DS in section 3.2.S.1.3 and 3.2.S.3.1 — The determined minimum solubility was — mg/mL. This results in only — mL of aqueous medium needed to dissolve the highest dosage strength of 300 mg of DS. b(4)

Data supporting high permeability:

A DS is considered highly permeable when it shows linear and complete absorption and when the extent of absorption in humans is determined to be >/=90% of an administered dose based on a mass balance determination or in comparison to an intravenous dose. Alternately, nonhuman systems (e.g., *in vitro* epithelial cells) capable of predicting the extent of drug absorption in humans can be used.

Sponsor's data from a mass balance trial with radiolabelled lacosamide (SP619) indicate and absorption of 95% of DS after oral administration and two comparative bioavailability trials (SP645 and SP658) show an absolute bioavailability of 100%.

Pharmacokinetic parameters of lacosamide in plasma from SP645 and SP658 are summarized below:

Pharmacokinetic parameters of lacosamide following single-dose administration of 200mg lacosamide as solution for infusion or tablet in healthy male subjects – SP645 and SP658

Trial	Drug formulation	N	$AUC_{(0-tz)}$ (µg/mL*h)	C_{max} (µg/mL)	t_{max} (h)
			Geometric mean (CV %)		Median (range)
SP645	Solution for infusion (15min)	16	72.3 (17.4)	5.7 (36.3)	0.25 (0.25-2.00)
	Tablet	16	73.6 (19.1)	4.8 (23.6)	0.75 (0.28-4.00)
SP658	Solution for infusion (30min)	24	78.3 (23.9)	5.8 (28.0)	0.50 (0.50-2.00)
	Solution for infusion (60min)	25	79.1 (24.8)	5.3 (22.5)	1.00 (1.00-3.00)
	Tablet	23	78.1 (24.0)	4.9 (27.9)	0.75 (0.25-4.00)

CV=coefficient of variation

The sponsor has also confirmed the high permeability of the DS in an vivo permeation study using Caco-2 monolayer method where the apparent permeability coefficient of lacosamide (160 nm/s) was shown to be higher than that of the standard, propranolol (118 nm/s).

Data supporting rapid and similar dissolution:

The sponsor quotes the recommendation of the FDA guidance with regard to this, i.e. an immediate-release drug product is considered rapidly dissolving when >/= 85% of the labeled amount of the drug dissolves within 30 minutes in a volume of </= 900 mL in each of the following media: 0.1N HCL pH 1.0, buffer pH 4.5 and buffer pH 6.8 Apparatus I at 100 rpm or Apparatus II at 50 rpm.

Therefore, the commercial tablet (test product) in strengths of 50, 100, and 300 mg was compared with the tablet used in clinical trials (reference product) in strengths of 50 mg and 100 mg. They performed dissolution experiments with n = 12 units in 3 different media at pH 1.0, pH 4.5 and pH 6.8 at 4 time points (10, 15, 20 and 30 minutes) in Apparatus II at 50 rpm.

For exemption from bioequivalence studies, *in vitro* data should demonstrate the similarity of dissolution profiles of test and reference products. Profiles should be compared using the similarity factor f_2 , which measures the closeness between 2 dissolution profiles. However, when >/= 85% of the labeled amount of the drug dissolves within 15 minutes in all 3 recommended dissolution media in both the test and the reference product, a profile comparison using the f_2 test is not necessary. To allow the use of mean data, the coefficient of variation (%) at earlier time points (i.e. 10 minutes) should not more than 20%. At other

time points, it should not be more than 10%. Data presented in the following tables and in appendix fulfill this requirement.

Evaluation

The sponsor has demonstrated that for all tested products and in all test media, >/= 85% of the labeled amount of lacosamide was released at 15 minutes, (complete data for all tested time points 10, 15, 20, and 30 minutes are presented in the sponsor's Appendix 3 of their 14 Dec 2007 submission).

The following table presents comparative dissolution testing results (more details presented in Appendix B):

Comparative dissolution testing of the commercial tablet with — film-coat (test) and the tablet used in clinical development (reference) at pH 1-6.8 (n = 12)

b(4)

	Drug dissolved at 15 minutes		
	Mean [%]	Range [%]	RSD [%]
Strength: 50 mg lacosamide			
Test product (50 mg, batch no. WE 13328 (P53100)):			
pH 1.0 (0.1 N HCl)	97		2.2
pH 4.5 (acetate buffer)	95		1.2
pH 6.8 (phosphate buffer)	94		2.6
Reference product (50 mg, batch no. 225250):			
pH 1.0 (0.1 N HCl)	96		2.4
pH 4.5 (acetate buffer)	96		4.0
pH 6.8 (phosphate buffer)	96		2.2
Strength: 100 mg lacosamide			
Test product (100 mg, batch no. WE 13311 (X50040)):			
pH 1.0 (0.1 N HCl)	94		4.6
pH 4.5 (acetate buffer)	94		2.1
pH 6.8 (phosphate buffer)	93		4.3
Reference product (100 mg, batch no. 0412200001):			
pH 1.0 (0.1 N HCl)	95		2.7
pH 4.5 (acetate buffer)	96		3.0
pH 6.8 (phosphate buffer)	96		2.5
Strength: 300 mg lacosamide			
Test product (300 mg, batch no. WE 13337 (P53110)): [a]			
pH 1.0 (0.1 N HCl)	91		5.1
pH 4.5 (acetate buffer)	93		4.5
pH 6.8 (phosphate buffer)	93		8.0

Method: Paddle apparatus, 900 mL 0.1 N HCl, 37 ± 0.5°C, 50 revolutions per minute

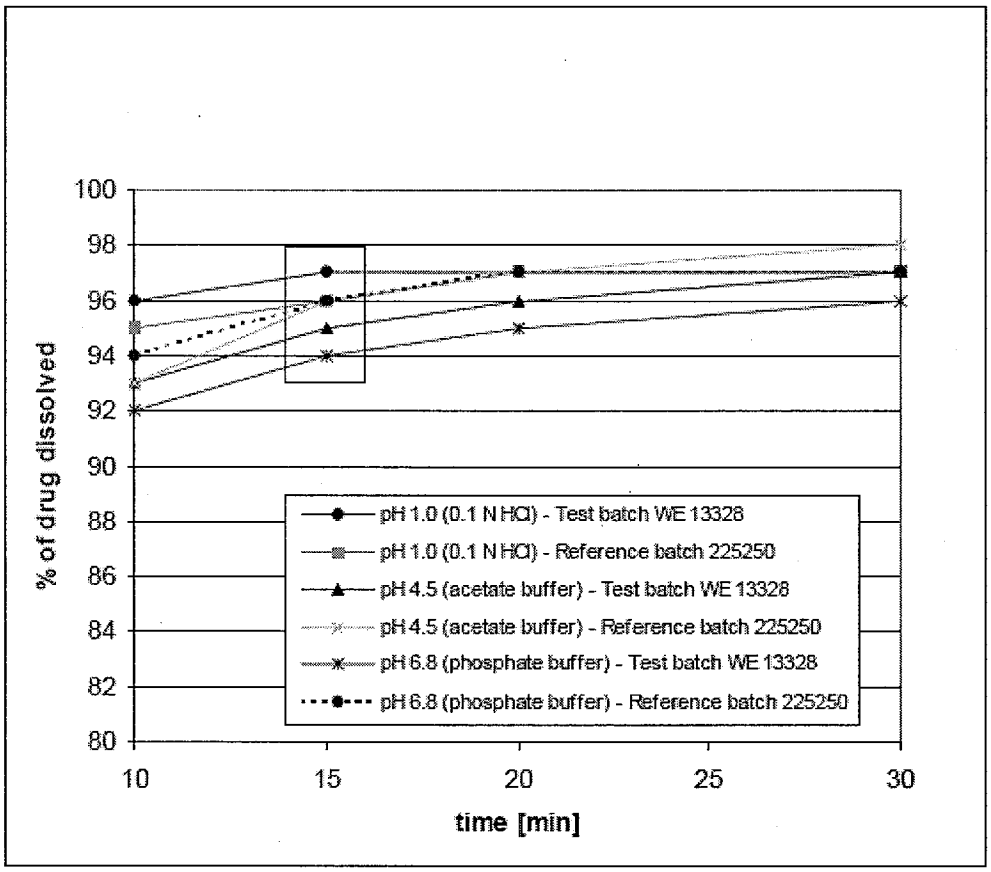
RSD = Relative standard deviation

a No tablet containing 300 mg lacosamide was developed for use in clinical trials. Therefore, the commercial tablet with the highest dosage strength was compared with the reference product with the highest available dosage strength, i.e., 100 mg.

The sponsor has also provided figures for the 50, 100 & 300 mg strengths comparing commercial and clinical tablet dissolution at different time points. The figures for the 50 mg and 300 mg tablet are reproduced below:

Comparative dissolution testing of the 50 mg commercial tablet with — film-coat (test) and the 50 mg tablet used in clinical development (reference) at pH 1-6.8 (n = 12)

b(4)



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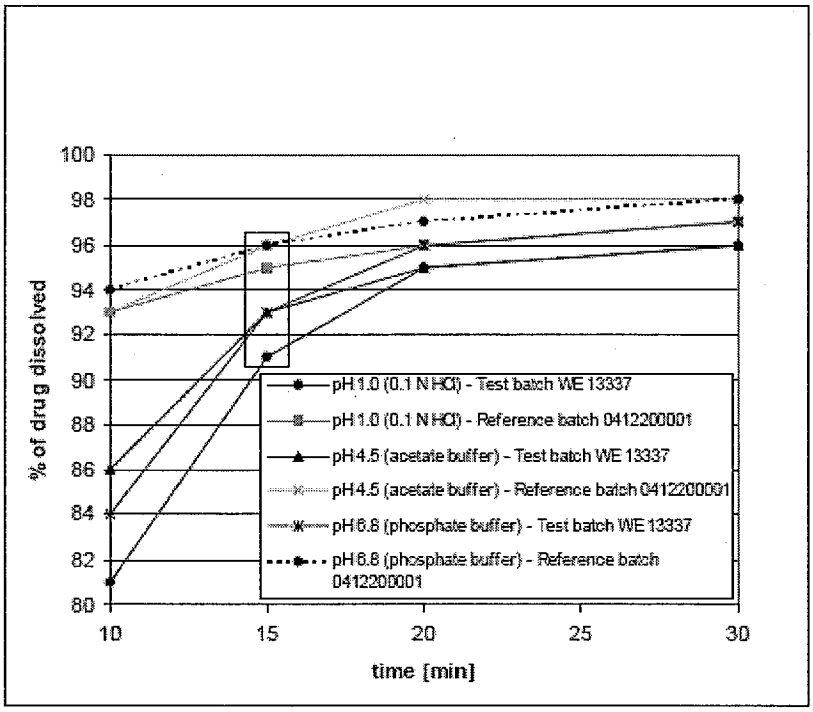
Comparative dissolution testing of the — mg commercial tablet with — film-coat (test) and the 100 mg tablet used in clinical development (reference) at pH 1-6.8 (n = 12)

b(4)



The figure for the 100 mg tablet is almost similar to the 50 mg tablet.

Conclusion

The sponsor concludes that the 50 & 100 mg tablets can be described as rapidly dissolving with similar dissolution profiles. The 300 mg commercial test product met the requirement for rapidly dissolving and it's dissolution profile was similar to the 100 mg tablet used in clinical trials; the sponsor did not develop a 300 mg tablet for use in clinical trials.

Evaluation

As a further requirement for exemption from bioequivalence studies (when >/=85% of drug dissolves in 15 minutes), the coefficient of variation (%) (RSD%) for each of the strengths was not more than 20% at 10 minutes and not more than 10% at other time (15, 20, & 30 min) points.

C.2 Commercial tablet formulation coated with different color-coats

b(4)

To demonstrate the similarity of dissolution profiles, the commercial formulation with the — film-coat (reference product) and the different color-coated tablets (test products) were investigated under the same conditions as described in paragraph. These batches had the different color-coats applied to identical tablet cores of 50 mg dosage strength and hence, evaluated only the potential effects of the different colors. The tabulated results are presented below:

b(4)

Comparative dissolution testing of the 50 mg commercial tablet with [redacted] (reference) versus the 50 mg commercial tablet with different color-coats (test) at pH 1-6.8 (n = 12)

	Drug dissolved at 15 minutes		
	Mean [%]	Range [%]	RSD [%]
Reference product: [redacted] film coated tablet, batch no. 20509009 (252310)			
pH 1.0 (0.1 N HCl)	96		3.8
pH 4.5 (acetate buffer)	100		1.4
pH 6.8 (phosphate buffer)	96		2.9
Test product: Pinkish film-coated tablet, batch no. 051			
pH 1.0 (0.1 N HCl)	98		6.7
pH 4.5 (acetate buffer)	98		5.1
pH 6.8 (phosphate buffer)	96		6.2
Test product: Dark yellow film-coated tablet, batch no. [redacted]0)			
pH 1.0 (0.1 N HCl)	98		4.2
pH 4.5 (acetate buffer)	100		1.5
pH 6.8 (phosphate buffer)	99		1.9
Test product: Salmon film-coated tablet, batch no. 051			
pH 1.0 (0.1 N HCl)	96		6.3
pH 4.5 (acetate buffer)	99		3.5
pH 6.8 (phosphate buffer)	98		2.0
Test product: Blue film-coated tablet, batch no. 051209			
pH 1.0 (0.1 N HCl)	100		3.5
pH 4.5 (acetate buffer)	98		5.3
pH 6.8 (phosphate buffer)	99		2.0

b(4)

Method: Paddle apparatus, 900 mL 0.1 N HCl, 37 ± 0.5°C, 50 revolutions per minute
RSD = Relative standard deviation

Results:

The [redacted] film-coated tablet formulations as well as the different color-coated tablets can be described as rapidly dissolving tablets with similar dissolution profiles. The [redacted] dye pigments [redacted] had no influence on the pharmaceutical characteristics, i.e. dissolution profile, of the tablets.

b(4)

For all products tested and in all media tested, >/=85% of the labeled amount of lacosamide was released at 15 minutes (shown in the table above). Complete data for all tested time points 10, 15, 20, and 30 minutes are presented in appendix 4 of this section in the NDA.

Evaluation

Like earlier results the coefficient of variation (%) (RSD%) for each of the color coated tablets was not more than 20% at 10 minutes and not more than 10% at other time (15, 20, & 30 min) points.

2.b. *In vivo* Dose Proportionality

Since the bioequivalence study was carried out with the 100 mg tablet and the highest compositionally proportional commercial strength is 300 mg establishment of *in vivo dose* proportionality would further justify the sponsor's request of a waiver of *in vivo* bioequivalence studies for the commercial formulation and higher strength tablets. *In vivo* dose proportionality was confirmed by the Clinical Pharmacology, Dr. Emmanuel Fadiran, reviewer in the following e-mail (dated 05-Mar-2008): b(4)

- Single Dose Proportionality Studies
  - Dose proportional from 100-800 mg QD
- Multiple-dose Proportionality Studies
  - Dose proportional from 100-200 mg & 200-500 mg BID

As I mentioned at the meeting the number of subjects in the 500 mg BID group is very small but I am comfortable to conclude that dose proportionally was shown for 100 to 800 mg QD and 100 to 300 BID.

Conclusion

The sponsor's request for a waiver of *in vivo* bioequivalence studies for the commercial formulation is justified based on the data presented by them, which demonstrate that the drug substance is BCS Class 1 (highly solubility and permeability), tablets are rapidly dissolving and presence of *in vivo* dose proportionality.

3. Bioavailability assessments

For the quantification of lacosamide and its main metabolite SPM 12809 in clinical trials, specific and sensitive liquid chromatography-mass spectrometry (LC-MS) methods were developed and validated using [redacted] internal standards. b(4)

The following table summarizes some key aspects of the bioanalytical methods (including list of supporting validation reports) used for the determination of concentration data in bioavailability and bioequivalence trials.

Bioanalytical methods used in bioavailability and bioequivalence trials

Trial	Matrix	Validation report	Analyte	LOQ µg/mL	Type of assay
SP619	Plasma/ urine/ feces	Methodology described in 5.3.1.1.1: SP619 CTR Section 6.7	[^{14}C]-ß-activity	30dpm above background[a]	Liquid scintillation counting, others
SP657	plasma	5.3.1.4.7: ikp094-04-05-he	LCM	0.1	LC-MS/MS
			SPM 12809	0.022	
	urine	5.3.1.4.7: ikp094-04-05-he	LCM	5.29	
			SPM 12809	1.14	
SP645	plasma	5.3.1.4.24: pc27528-1	LCM	0.1	
SP658	plasma	5.3.1.4.10: ba583-03	LCM	0.01	
			SPM 12809	0.01	
SP600	plasma	5.3.1.4.4: [redacted]a215	LCM	0.1	
	urine		LCM	5.0	

CTR=Clinical Trial Report; dpm=disintegrations per minute; LC-MS/MS=liquid chromatography coupled with tandem mass spectromerry; LCM=lacosamide; LOQ=lower limit of quantification

a This is the limit of reliable determination.

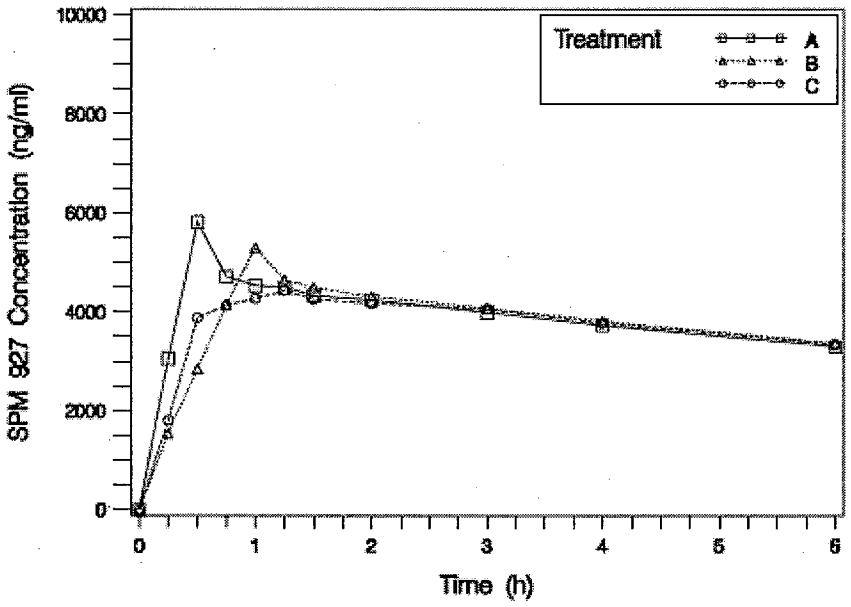
b(4)

3. a. Comparison of the clinical trial tablet to the solution given as 30-min and 60-min infusion

- The clinical trial tablet is bioequivalent to the solution for infusion administered over 30 or 60 minutes (Study SP658).
- The clinical trial tablet is bioinequivalent to the solution for infusion administered over 15 min (Study SP658) due to differences in Cmax.

The following plasma concentration data (from Study SP658) were obtained for the three treatments and it is noteworthy that the rate of lacosamide absorption from the tablet formulation is similar to that from the 30- and 60 min infusion suggesting that the absorption rate from the tablets (although first order) is bracketed by the 0.17 mg/mL/min and 0.33 mg/mL/min iv infusion input rates and is clearly less than that achieved with the 15 min infusion (0.66 mg/mL/min).

Mean plasma concentration-time curves of lacosamide for Treatments A (N=24), B (N=25), and C (N=23) – 0-6 hours



SPM 927=lacosamide

Where:
Treatment A (test 1): 200 mg lacosamide in 20 mL as iv infusion over 30 minutes
Treatment B (test 2): 200mg lacosamide I 20 mL as iv infusion over 60 minutes
Batch number of bulk product: 20030154
Treatment C (reference): 200mg lacosamide as oral tablet (2 tablets of 100mg)

A summary of the mean pharmacokinetic parameters are presented in the following table:

Pharmacokinetic parameters after intravenous or oral administration of 200mg lacosamide (PK Set)

Parameter (Unit)	Treatment		
	A (N=24)	B (N=25)	C (N=23)
$AUC(0\text{-}t_z)$[a] (µg/mL*h)	80.2±16.6 (35.5-112.4)	81.2±17.6 (35.1-116.2)	80.1±17.6 (38.4-123.4)
C_{max}[a] (µg/mL)	6.0±1.5 (2.8-8.5)	5.4±1.1 (2.8-7.2)	5.1±1.4 (2.4-8.5)
$AUC(0\text{-}\infty)$[a] (µg/mL*h)	81.8±17.7 (35.9-118.5)	82.8±18.8 (35.5-122.9)	81.7±19.0 (38.9-131.4)
t_{max}[b] (h)	0.50 (0.50-2.00)	1.00 (1.00-3.00)	0.75 (0.25-4.00)
$t_{1/2}$[b] (h)	11.4 (9.3-17.0)	11.3 (9.5-17.2)	11.2 (9.3-18.0)
λ_z[b] (1/h)	0.0610 (0.0408-0.0749)	0.0614 (0.0404-0.0730)	0.0622 (0.0385-0.0746)
CL_{tot}[a,c] (L/h)	2.59±0.76 (1.69-5.57)	2.57±0.78 (1.63-5.64)	2.59±0.72 (1.52-5.14)

Treatment key: A=iv 30-minute infusion; B=iv 60-minute infusion; C=oral administration

[a] Arithmetic mean±standard deviation (range)

[b] Median (range)

[c] Clearance of lacosamide is given as total clearance (CL_{tot}) after iv administration and as total apparent clearance (CL_{tot}/f) after oral administration (see list of PK parameters in Section 4.1).

Data source: Table 9.4

Treatment ratios for primary pharmacokinetic parameters (relative bioavailability)

Parameter	Treatment ratios (mean±SD)	
	A/C	B/C
$AUC(0\text{-}t_z)$	1.00±0.06	1.00±0.07
C_{max}	1.17±0.25	1.04±0.14

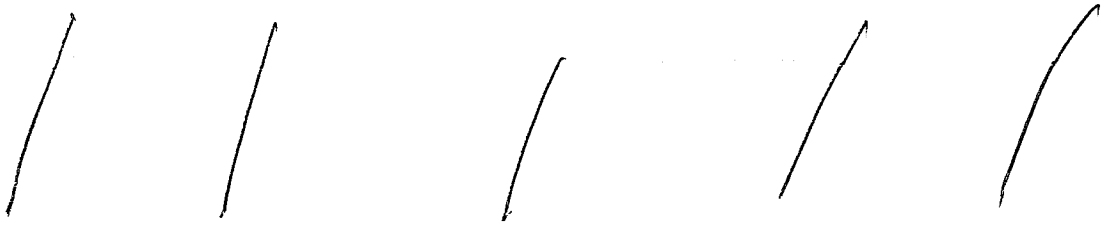
Treatment key: A=iv 30-minute infusion; B=iv 60-minute infusion; C=oral administration

Data source: Table 9.2 and Table 9.3

In summary, the results of this trial indicate that the pharmacokinetics of lacosamide are similar when lacosamide is given as 30-minute infusion, 60-minute infusion, or as tablet and that the lacosamide solution for infusion administered over 30 or 60 minutes is bioequivalent to the oral tablet.

b(4)

3. b.



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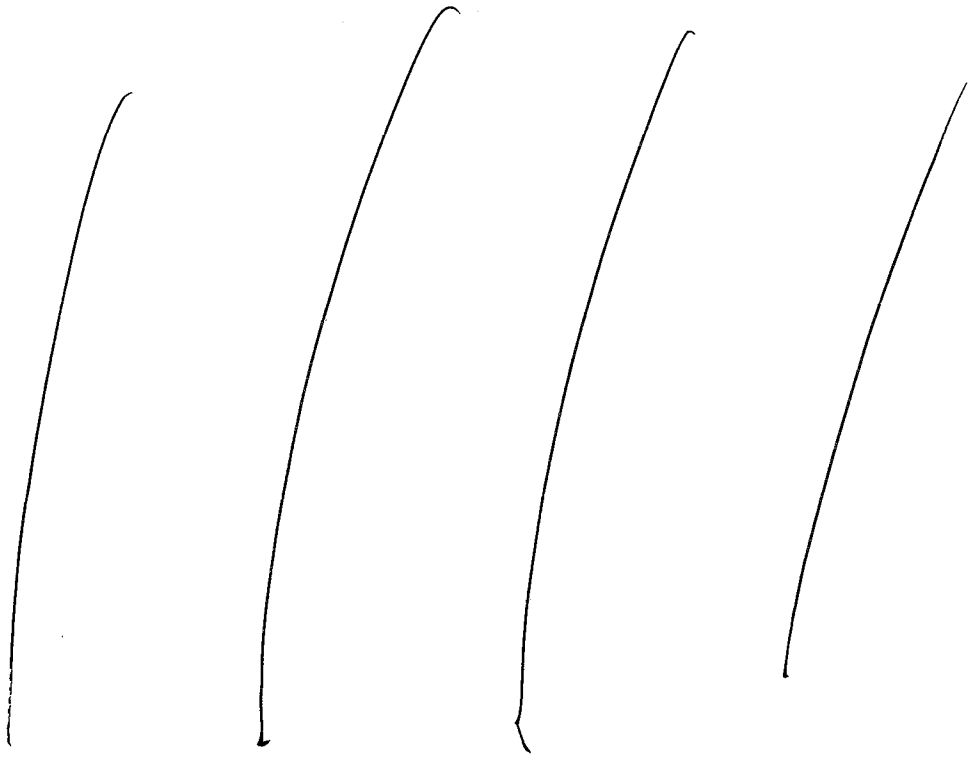
✓ Trade Secret / Confidential (b4)

_____ Draft Labeling (b4)

_____ Draft Labeling (b5)

_____ Deliberative Process (b5)



b(4)

4. Summary

The submitted *in vitro* dissolution data, coupled with BCS 1 classification of the drug substance, dissolution characteristics of the drug product, support adequacy of *in vitro* bioequivalence assessment of the proposed commercial tablet to the tablets studied in the clinical trials.

The Sponsor has provided adequate *in vitro* and in vivo characterization of the various lacosamide formulations, and adequate data to support their biowaiver requests for the *in vivo* assessment of the lacosamide proposed commercial tablets (50-mg, 100-mg, 150-mg, 200-mg, 250-mg and 300-mg strengths) b(4)

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APPENDIX A

QUANTITATIVE COMPOSITION OF THE COMMERCIAL TABLETS

Quantitative composition per film-coated tablet

Component	Reference to standard	Function	50 mg pinkish [mg]	100 mg dark yellow [mg]	150 mg salmon [mg]	200 mg blue [mg]	250 mg [mg]	300 mg [mg]
Lacosamide	In-house	Active ingredient	50.00	100.00	150.00	200.00		
Cellulose, microcrystalline	USP-NF							
Crospovidone	USP-NF							
Magnesium stearate	USP-NF							
Hydroxy-propylcellulose	USP-NF							
Total (film-coated tablet)			126.00	252.00	378.00	504.00		

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Quantitative composition of [redacted]

The comparison between the Clinical and Commercial formulation is shown below:

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Comparison of clinical trial and commercial (proportional) formulation (exemplary for a 100 mg dosage strength)

Ingredient	Function	Clinical trial formulation [mg]	Commercial formulation [mg]
Lacosamide	Active substance	100.00	100.00
Cellulose, microcrystalline			
Hypromellose			
Hydroxypropyl cellulose			
Crospovidone			
Magnesium stearate			

b(4)

The capsule formulations are given below:

Capsules filled with pure drug substance

Ingredient	Function	Capsule 50 mg dosage strength [mg]	Capsule 100 mg dosage strength [mg]	Capsule 200 mg dosage strength [mg]
Lacosamide	Active substance	50.00	100.00	200.00
Hard gelatin capsule	Capsule shell			

b(4)

Capsules filled with powder blend

Ingredient	Function	Capsule 50 mg dosage strength [mg]	Capsule 100 mg dosage strength [mg]	Capsule 200 mg dosage strength [mg]
Lacosamide	Active substance	50.00	100.00	200.00
Magnesium stearate				
Hard gelatin capsule	Capsule shell			

b(4)

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APPENDIX B

b(4)

Comparative dissolution testing of the commercial tablet formulation with [redacted] film-coat (test) and the tablet used in clinical development (reference) at pH 1 – 6.8 (n = 12) – strength: 50 mg lacosamide

Test product – batch no. WE 13328 (P53100)									
	pH 1.0 (0.1 N HCl)			pH 4.5 (acetate buffer)			pH 6.8 (phosphate buffer)		
Time	Mean [%]	Range [%]	RSD [%]	Mean [%]	Range [%]	RSD [%]	Mean [%]	Range [%]	RSD [%]
10 minutes	96	[redacted]	2.4	93	[redacted]	1.7	92	[redacted]	3.4
15 minutes	97		2.2	95		1.2	94		2.6
20 minutes	97		1.8	96		1.2	95		2.3
30 minutes	97		1.7	97		1.1	96		2.0
Reference product – batch no. 225250									
	pH 1.0 (0.1 N HCl)			pH 4.5 (acetate buffer)			pH 6.8 (phosphate buffer)		
Time	Mean [%]	Range [%]	RSD [%]	Mean [%]	Range [%]	RSD [%]	Mean [%]	Range [%]	RSD [%]
10 minutes	95	[redacted]	2.6	93	[redacted]	5.4	94	[redacted]	2.5
15 minutes	96		2.4	96		4.0	96		2.2
20 minutes	97		2.2	97		3.3	97		2.2
30 minutes	97		2.1	98		2.5	97		2.0

b(4)

b(4)

Comparative dissolution testing of the commercial tablet formulation with [redacted] film-coat (test) and the tablet used in clinical development (reference) at pH 1 – 6.8 (n = 12) – strength: 100 mg lacosamide

Test product – batch no. WE 13311 (X50040)									
	pH 1.0 (0.1 N HCl)			pH 4.5 (acetate buffer)			pH 6.8 (phosphate buffer)		
Time	Mean [%]	Range [%]	RSD [%]	Mean [%]	Range [%]	RSD [%]	Mean [%]	Range [%]	RSD [%]
10 minutes	87	[redacted]	9.6	89	[redacted]	5.5	87	[redacted]	8.1
15 minutes	94		4.6	94		2.1	93		4.3
20 minutes	97		2.3	96		1.1	96		2.4
30 minutes	98		1.8	96		1.5	97		1.6
Reference product – batch no. 0412200001									
	pH 1.0 (0.1 N HCl)			pH 4.5 (acetate buffer)			pH 6.8 (phosphate buffer)		
Time	Mean [%]	Range [%]	RSD [%]	Mean [%]	Range [%]	RSD [%]	Mean [%]	Range [%]	RSD [%]
10 minutes	93	[redacted]	3.3	93	[redacted]	5.1	94	[redacted]	3.0
15 minutes	95		2.7	96		3.0	96		2.5
20 minutes	96		2.5	98		2.7	97		2.4
30 minutes	97		2.4	98		2.2	98		2.3

b(4)

b(4)

b(4)

Comparative dissolution testing of the commercial tablet formulation with [redacted] film-coat (test) and the tablet used in clinical development (reference) at pH 1 – 6.8 (n = 12) – strength: 300 mg lacosamide

Test product – batch no. WE 13337 (P53110)[a]									
	pH 1.0 (0.1 N HCl)			pH 4.5 (acetate buffer)			pH 6.8 (phosphate buffer)		
Time	Mean [%]	Range [%]	RSD [%]	Mean [%]	Range [%]	RSD [%]	Mean [%]	Range [%]	RSD [%]
10 minutes	81	[redacted]	10.1	86	[redacted]	9.1	84	[redacted]	12.5
15 minutes	91		5.1	93		4.5	93		8.0
20 minutes	95		3.1	95		2.2	96		5.5
30 minutes	96		1.5	96		2.1	97		3.9

b(4)

RSD = Relative standard deviation

a No tablet containing 300 mg lacosamide was developed for use in clinical trials. Therefore, the commercial tablet with the highest dosage strength was compared with the reference product with the highest available dosage strength, i.e. 100 mg.

Comparative dissolution testing of the 50 mg commercial tablet formulation with — (reference) versus the 50 mg commercial tablet formulation with different color-coats (test) at pH 1 – 6.8 (n = 12)

Reference product: — film-coated tablet, batch no. 20509009 (252310)									
	pH 1.0 (0.1 N HCl)			pH 4.5 (acetate buffer)			pH 6.8 (phosphate buffer)		
Time	Mean [%]	Range [%]	RSD [%]	Mean [%]	Range [%]	RSD [%]	Mean [%]	Range [%]	RSD [%]
10 minutes	90		4.3	97		1.7	94		3.3
15 minutes	96		3.8	100		1.4	96		2.9
20 minutes	97		3.5	100		1.4	97		2.9
30 minutes	99		2.8	100		1.6	98		2.6
Test product: Pinkish film-coated tablet, batch no. 0512090003 (P53740)									
	pH 1.0 (0.1 N HCl)			pH 4.5 (acetate buffer)			pH 6.8 (phosphate buffer)		
Time	Mean [%]	Range [%]	RSD [%]	Mean [%]	Range [%]	RSD [%]	Mean [%]	Range [%]	RSD [%]
10 minutes	88		15.0	93		10.1	91		12.3
15 minutes	98		6.7	98		5.1	96		6.2
20 minutes	101		2.8	99		1.8	99		2.2
30 minutes	101		1.1	100		1.6	99		1.7

b(4)

b(4)

Test product: Dark yellow film-coated tablet, batch no. 0512090002 (P53730)									
	pH 1.0 (0.1 N HCl)			pH 4.5 (acetate buffer)			pH 6.8 (phosphate buffer)		
Time	Mean [%]	Range [%]	RSD [%]	Mean [%]	Range [%]	RSD [%]	Mean [%]	Range [%]	RSD [%]
10 minutes	91		9.7	96		6.4	96		5.3
15 minutes	98		4.2	100		1.5	99		1.9
20 minutes	99		2.7	100		1.3	99		1.8
30 minutes	99		1.5	100		1.2	99		1.6
Test product: Salmon film-coated tablet, batch no. 0512090001 (P53720)									
	pH 1.0 (0.1 N HCl)			pH 4.5 (acetate buffer)			pH 6.8 (phosphate buffer)		
Time	Mean [%]	Range [%]	RSD [%]	Mean [%]	Range [%]	RSD [%]	Mean [%]	Range [%]	RSD [%]
10 minutes	94		6.0	96		6.4	94		8.1
15 minutes	96		6.3	99		3.5	98		2.0
20 minutes	99		1.8	100		1.8	99		1.4
30 minutes	99		1.7	101		2.0	99		1.5

b(4)

b(4)

Similar tables are also given for the three additional colors, blue, — which show similar data.

b(4)

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APPENDIX D

Drug formulation information

Drug formulation	Composition	Use in clinical trials
Capsule hand-filled with pure drug substance	Active ingredient: LCM No inactive ingredients	Phase 1: SP835, SP836 Phase 2/3: Partial-onset seizures: SP586
Capsule filled with powder blend	Active ingredient: LCM Inactive ingredients: magnesium stearate	Phase 1: SP587, SP588, SP599, SP601, SP602, SP603, SP618 Phase 2/3: Partial-onset seizures: SP598 Neuropathic pain: SP611
Tablet	Active ingredient: LCM Inactive ingredients: Microcrystalline cellulose, crospovidone, , magnesium stearate, hypromellose hydroxypropylcellulose, polyethylene glycol, titanium dioxide,	Phase 1: SP600, SP620, SP640, SP641, SP642, SP643, SP644, SP645, SP657, SP658, SP660, SP661, SP863, SP903 Phase 2/3: Partial-onset seizures: SP607, SP615, SP616, SP667, SP754, SP755, SP756, SP774 Neuropathic pain: SP614, SP647, SP655, SP665, SP690, SP742, SP743, SP745, SP746, SP768, SP830, SP746 subtrial
Commercial tablet	Active ingredient: LCM Inactive ingredients: Microcrystalline cellulose, hydroxypropylcellulose, colloidal silicon dioxide, crospovidone, magnesium stearate Polyvinyl alcohol, polyethylene glycol, talc, lecithin, hypromellose, titanium dioxide	Used for stability testing only, not used in clinical trials

b(4)

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Drug formulation	Composition	Use in clinical trials
Commercial tablet (colored)	Active ingredient: LCM Inactive ingredients: Microcrystalline cellulose, hydroxypropylcellulose, colloidal silicon dioxide, crospovidone, magnesium stearate Polyvinyl alcohol, polyethylene glycol, talc, lecithin, hypromellose, titanium dioxide and iron oxide(s) and/or indigo carmine aluminum lake	Used for stability testing only, not used in clinical trials
Solution for infusion	Active ingredient: LCM Inactive ingredients: Sodium chloride, water for injection, 0.1N HCl (pH adjustment)	Phase 1: SP643, SP645, SP658 Phase 2/3: Partial-onset seizures: SP616, SP757
[^{14}C] solution for infusion	Active ingredient: [^{14}C]- LCM and unlabeled LCM Inactive ingredients: 0.9% sodium chloride	Phase 1: SP619
[^{14}C] oral solution	Active ingredient: [^{14}C]- LCM and unlabeled LCM Inactive ingredients: 0.9% sodium chloride	Phase 1: SP619

b(4)

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LCM=lacosamide

Note: The batch numbers used in the individual trials are shown in Appendix 2.7.1.4.3.

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BIOPHARMACEUTICS

Office of Clinical Pharmacology
New Drug Application Filing and Review Form

General Information About the Submission

	Information		Information
NDA Numbers	22-253, 22-254 [redacted] (Neuro) & [redacted] (DAARP)	Brand Name	No proposed trade name
OCP Division (1, 2, 3, 4, 5)	DCP 2	Generic Name	Lacosamide
Medical Divisions	DAARP	Drug Class	
OCP Reviewer	Emmanuel O Fadiran	Indication(s)	• Diabetic Peripheral Neuropathic (DPN) • Partial onset seizures
OCP Team Leader	Suresh Doddapaneni	Dosage Forms/Strength	• Film-coated tablets – 50, 100, 150, 200, 250, 300 mg • [redacted] • Injection – 10 mg/ ml
		Dosing Regimen	
Date of Submission	09/28/2007	Route of Administration	Oral /IV
Estimated Due Date of OCP Review	05/26/2008	Sponsor	Schwarz Biosciences, Inc
PDUFA Due Date	07/28/2008	Priority Classification	S
Division Due Date	05/26/2008	Submission Type	NME

Clin. Pharm. and Biopharm. Information

	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	x			
Tabular Listing of All Human Studies	x			
HPK Summary	x			
Labeling	x			
Reference Bioanalytical and Analytical Methods	x			
I. Clinical Pharmacology				
Mass balance:	x	1		
Isozyme characterization:	x	6		
Blood/plasma ratio:	x	1		
Plasma protein binding:	x	2		
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				
single dose:	x	3		
multiple dose:	x	2		
Patients-				
single dose:	x	2		
multiple dose:	x	2		
Dose proportionality -				
fasting / non-fasting single dose:	x	2		
fasting / non-fasting multiple dose:	x	2		
Drug-drug interaction studies -				
In-vivo effects on primary drug:	x	3		
In-vivo effects of primary drug:	x	6		
In-vitro:				
Subpopulation studies -				
ethnicity:	x	1		
gender:	x	1		
pediatrics:	x	1		
geriatrics:	x	1		
renal impairment:	x	1		
hepatic impairment:	x	1		
PD:				
Phase 2:	x	3		

Phase 3:				
PK/PD:				
Phase 1 and/or 2, proof of concept:	x			
Phase 3 clinical trial:	x			
Population Analyses -				
Data rich:	x	2		
Data sparse:	x	3		
II. Biopharmaceutics				
Absolute bioavailability:	x	1		
Relative bioavailability -				
solution as reference:				
alternate formulation as reference:				
Bioequivalence studies -				
traditional design; single / multi dose:	x	3		
replicate design; single / multi dose:				
Food-drug interaction studies:	x	1		
Dissolution:	x			
(IVIVC):				
Bio-wavier request based on BCS	x			
BCS class	x			**BCS 1**
III. Other CPB Studies				
Genotype/phenotype studies:	x	1		
Abuse potential	x	1		
Pediatric development plan				
QTc	x	1		
Total Number of Studies		33		

Filability and QBR comments		
	"X" if yes	Comments
Application filable?	x	• See below.
Comments sent to firm?		1. Please submit the applicable data from the following to support the population PK analyses and concentration-response relationship analyses: •All datasets used for model development and validation should submitted as SAS transport files (*.xpt). A description of each data should be provided in a Define.pdf file. Any concentrations and/or subj that have been excluded from the analysis should be flagged and mainta in the datasets. •Model codes or control streams and output listings should be provided all major model building steps, e.g., base structural model, covari models, final model, and validation model. These files should be subm as ASCII text files with *.txt extension (e.g.: myfile_ctl.txt, myfile_out.t •A model development decision tree and/or table which gives an over of modeling steps. For the population analysis reports we request that you submit, in addition to the standard model diagnostic plots, individual plots for a representative number of subjects. Each individual plot should include observed concentrations, the individual prediction line and the population prediction line. In the report, tables should include model parameter names and units. For example, oral clearance should be presented as CL/F (L/h) and not as THETA(1). Also provide in the summary of the report a description of the clinical application of modeling results. 2. Under individual subject listing for each study, the data listing dataset folder has numerous datasets. The definition of these data sets should be provided. We acknowledge the definition of the data columns within these data sets has been provided, but description of datasets like ALCO, CAFF etc have not been provided. Under analysis dataset, the description of PC, PP and PC-E have not been given. 3. The PK-PD modeling report for epilepsy is not under the Folder 5.3.4 (reports for human PD studies). Neither is it present in the tabular listing of all studies. It was found in the Folder 5.3.5 (reports for efficacy and safety studies). Please verify that all studies/ Modeling reports submitted to the NDA are listed under the Tabular listing of studies.
QBR questions (key issues to be considered)		• Is the metabolism (*in vitro and in vivo)* of lacosamide well characterized? • Are appropriate drug-drug interaction studies conducted? • Is there an E-R relationship for DNP? • Are there important covariates that affect PK of lacosamide? • Are there exposure data in special populations for labeling? • Are the information on the PK and E-R in the labeling appropriate?

Pending thorough review of the data, following is the Clinical Pharmacology information submitted to the NDAs-

Background:

Lacosamide (LCM; SPM 927; previously referred to as harkoseride; [R]-2-acetamido-N-benzyl-3-methoxypropionamide, ADD 234037) is a member of a series of functionalized amino acids that were specifically synthesized as anticonvulsant drug candidates. Electrophysiological studies have shown that LCM enhances the slow inactivation of

sodium channels by attenuating the proportion of available channels in a time- and voltage-dependent manner. This leads to a reduction of sodium channel long-term availability which increases activation thresholds and reduces hyperexcitability of neurons characteristic for both epilepsy and neuropathic pain. This is a novel mode of action since other sodium channel modulators such as lamotrigine, phenytoin, and carbamazepine enhance fast inactivation with no or small effects on slow inactivation. In addition, it has been shown that LCM interacts with collapsing response mediator protein 2 (CRMP-2), a protein involved in neuronal differentiation and control of axon outgrowth. The interaction of LCM with CRMP-2 represents a second mode of action of LCM.

LCM is being developed for the treatment of adults with diabetic neuropathic pain (DNP) and patients with partial-onset seizures. Overall, LCM has been studied in the following:
- 24 Phase 1 trials
- 6 completed and 3 ongoing Phase 2/3 trials for the treatment of subjects with DNP
- 2 completed Phase 2/3 trials for the treatment of subjects with post-herpetic neuralgia
- 1 completed and 1 ongoing Phase 2/3 trial for the treatment of subjects with mixed neuropathic pain
- 8 completed and 3 ongoing Phase 2/3 trials for adjunctive treatment for subjects with partial-onset seizures

The 9 clinical trials that evaluated the efficacy of LCM as oral therapy in adult subjects with DNP include 3 primary double-blind, placebo-controlled, parallel-design trials (SP742, SP743, and SP768), 1 primary double-blind, withdrawal-design trial (SP746 controlled), 1 supporting trial (SP614), and 1 completed (SP665) and 3 ongoing trials (SP745, SP746, and SP830) evaluating long-term efficacy. These 9 trials are summarized in Table 1 below.

Table 1: Summary of Efficacy and Safety Studies of LCM in adults with DNP

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Protocol number	Trial design	LCM dose	Maximum treatment duration	Total number of subject exposures to LCM
Primary efficacy trials				
Parallel-group design				
SP742	Multicenter, DB, PC	200, 400, and 600mg/day	20 weeks	277
SP743	Multicenter, DB, PC	400 and 600mg/day	20 weeks	283
SP768	Multicenter, DB, PC	200, 400, and 600mg/day	20 weeks	403
Controlled withdrawal design				
SP746 controlled	Multicenter, DB, PC	Up to 400mg/day	16 weeks	106[a]
Supporting efficacy trial				
SP614	Multicenter, DB, PC	Up to 400mg/day	10 weeks	60
Long-term efficacy trials				
SP665	Multicenter, OL, UC	Up to 400mg/day	939 days	69[a]
SP745	Multicenter, OL, UC	Up to 600mg/day	Approximately 2 years	451[a]
SP746	Multicenter, OL, UC	Up to 600mg/day	Approximately 2 years, 4 months	214[a]
SP830	Multicenter, OL, UC	Up to 600mg/day	Approximately 1 year, 9 months	371

DB=double-blind; DNP=diabetic neuropathic pain; LCM=lacosamide; OL=open-label; PC=placebo-controlled; UC=uncontrolled

a These numbers do not represent unique exposures as a subject may have participated in more than 1 trial.

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Note that the primary efficacy withdrawal-design trial, SP746 controlled, has been referred to as the SP746 subtrial in other documents for this submission. However, for this evaluation of

Dose-response and dose selection

SP742 and SP768 evaluated the efficacy and safety of LCM (200, 400, and 600mg/day) versus placebo and thus, these trials meet the ICH definition of dose-response trials. In SP742,

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Drug Product and Formulations used for clinical studies

Lacosamide 50 mg, 100 mg, 150 mg, 200 mg, 250 mg and 300 mg film-coated tablets are different colored, oval, ablets of different size and are compositionally proportional formulations (Table 2). b(4)

Table 2: Quantitative composition per film-coated tablet

Component	Reference to standard	Function	50 mg pinkish [mg]	100 mg dark yellow [mg]	150 mg salmon [mg]	200 mg blue [mg]	250 mg [mg]	300 mg [mg]
Lacosamide	In-house	Active ingredient	50.00	100.00	150.00	200.00	250.00	300.00
Cellulose, microcrystalline	USP-NF							
Crospovidone	USP-NF							
Magnesium stearate	USP-NF							
Hydroxy-propylcellulose	USP-NF							
Total (film-coated tablet)			126.00	252.00	378.00	504.00		

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Because of its high solubility in terms of the BCS, and high permeability demonstrated in absolute bioavailability studies and *in vitro* experiments, lacosamide is classified as a BCS class 1 drug substance (see below).

The first clinical trials were supplied with hard gelatin capsules size which were hand filled with 50 mg, 100 mg or 200 mg of the pure drug substance lacosamide. Later, a capsule formulation containing a blend of lacosamide with excipients was developed

, an film-coated IR tablet was developed. This tablet, used in all clinical trials thereafter, is a oval tablet, identical in size for tablets containing 50 mg and 100 mg of drug substance to allow for blinding. Table 3 shows a comparison of the 100 mg LCM formulations.

Table 3: Comparison of the 100 mg LCM formulations

Overview on the different formulations (exemplary for a 100 mg dosage strength)

Ingredient	Capsule [mg]	Capsule with powder-blend [mg]	Clinical trial formulation [mg]	Commercial formulation (proportional) [mg]
Lacosamide	100.00	100.00	100.00	100.00
Cellulose, microcrystalline				
Hydroxypropyl cellulose				
Hypromellose				
Crospovidone				
Magnesium stearate				
Titanium dioxide				

Commercial tablet formulation with film-coat

In order to demonstrate the similarity of dissolution profiles, the commercial tablet formulation (test product) in strengths of 50 mg, 100 mg, and 300 mg was compared with the tablet used in clinical trials (reference product) in strengths of 50 mg and 100 mg. Dissolution experiments with n = 12 units in 3 different media at pH 1.0, pH 4.5 and pH 6.8 were performed at 4 time points (10, 15, 20, and 30 minutes) in Apparatus II at 50 rpm.

Request for Waiver of *In Vivo* Bioequivalence Study for ——— capsules used in early development studies and commercial tablet b(4)

As mentioned above, capsule formulations were used for some of the early development studies and the commercial tablet that will be marketed is slightly different from the tablet used in clinical development. Both formulations are IR film-coated tablets which differ in size, shape, and color.

The Sponsor has requested waiver of BE study for these formulations based on the classification of LCM as a BCS Class 1 drug based the following:

- minimum solubility of ~ ug/mL, only ~ of water is needed to dissolve the highest dosage strength of 300mg of drug substance
- absorption of LCM of approximately 94% after oral administration. Comparative bioavailability trials (SP645 and SP658) show an absolute bioavailability of approximately 100% when LCM was administered as tablet in comparison to an iv reference dose
- *in vitro* permeation studies across a monolayer of epithelial cells (Caco-2 monolayer) were performed with LCM using propranolol as a highly permeable reference standard. The apparent permeability coefficients for the transport of propranolol and LCM in the apical to basolateral direction were higher for LCM than for propranolol.

The waiver request will be reviewed by the ONDQA.

Summary of Results of Clin Pharm studies

Plasma protein binding

The binding of [^{14}C]-LCM to plasma proteins was determined *in vitro* by equilibrium dialysis with human plasma in a concentration range of 1.5 to 60µg/mL [^{14}C]-LCM. The overall mean plasma protein binding of [^{14}C]-LCM was 6.1%. Mean blood cell partitioning of [^{14}C]-LCM was 54%. No concentration-dependent trends were observed. Study 9827351 investigated the binding of LCM to human plasma proteins in selected ultrafiltrate samples from SP834 following intravenous administration of 50, 100, 150, or 300 mg LCM per subject. At LCM plasma concentrations of 0.7 to 5.5µg/mL, plasma protein binding was <15%, confirming that binding of LCM to plasma proteins is low.

In vitro metabolism of LCM

Study 9818851 investigated the *in vitro* metabolism of LCM using hepatic microsomes. In human liver microsomes, no biotransformation of LCM was observed. The study suggests that oxidative metabolism via cytochrome P450 plays a minor part in the hepatic clearance of LCM.

Study 0699/025 investigated the metabolism of [^{14}C]-LCM in hepatocytes isolated from man. Two major metabolites (SPM 12809 [desmethyl-metabolite] and SPM 6912 [desacetyl-metabolite]) and minor polar components were detected in *in vitro* incubations in human hepatocytes.

Study 688 investigated the metabolism of [^{14}C]-LCM in human liver and kidney microsomes, in human plasma, and using recombinant CYP2C19. Less than 10% of [^{14}C]-LCM was metabolized in the different *in vitro* models. The results for human

CYP2C19 microsomes indicated that CYP2C19 is able to catalyze the metabolism of LCM.

In vitro induction and inhibition of CYP isoforms
Studies BA 555-02 and 732 investigated the potential of LCM to induce CYP enzyme activity in cryopreserved human hepatocytes from male and female human donors. LCM showed no potential to induce the activity of CYP1A2 but a slight induction of CYP3A4 in 1 of 2 donors was noted at 500µmol/L (125µg/mL) in the presence of acetonitrile as vehicle. In study 732, human hepatocytes treated with LCM at concentrations of 50µmol/L (12.5µg/mL) and 500µmol/L (125µg/mL) did not show a significant induction of any of the tested CYP isoforms (1A2, 2B6, 2C9, 2C19, and 3A4). Studies M1999-057, BA 481-03, and 865 investigated the potential of LCM to inhibit CYP enzyme activity *in vitro*. In study M1999-057, which evaluated 7 CYP isoforms (1A2, 2A6, 2C9, 2C19, 2D6, 2E1, and 3A4) in cryopreserved human hepatocytes, LCM showed no potential to inhibit the activity of CYP isoforms at a LCM concentration of 100µmol/L (25µg/mL), except for CYP2C19 for which an inhibition of 59.9±6.2% (mean ± standard deviation) was determined. In study BA 481-03, the potential of LCM and SPM 12809 to inhibit CYP isoforms was evaluated using recombinant human enzymes. No or low inhibitory interactions of LCM and SPM 12809 with CYP1A2, 3A4, 2C9, and 2D6 isoforms were detectable. CYP2C19, 3A4, and 2C9 were inhibited by LCM but not by SPM 12809. The median inhibitory concentrations (IC50) of 1.8, 2.8, and 10.2mmol/L (450, 700, and 2550µg/mL) markedly exceed human plasma levels of 14.5µg/mL after oral administration of 300mg twice daily (SP588).
No inhibitory interactions with CYP2A6, 2B6, 2C8, and 2E1 were detectable for LCM or SPM 12809. CYP1A1 was inhibited by LCM with an IC50 value of 47.8 mmol/L (11950µg/mL) but not by SPM 12809 (Study 865). The IC50 values for the inhibition of CYP3A5 by LCM and SPM 12809 were calculated to be 3.31 and 6.20 mmol/L (830 and 1460µg/mL), respectively which markedly exceed human plasma levels of 14.5µg/mL after oral administration of 300 mg twice daily (SP588).

In vitro transport processes
Transport of LCM across Caco-2 monolayers, the involvement of P-glycoprotein, and the potential modulation of digoxin transport were investigated. It was found that LCM is not a substrate for P-glycoprotein, and does not modulate the transport of digoxin at concentrations up to 3mmol/L (750µg/mL).

Pharmacokinetics and pharmacodynamics of LCM in healthy subjects
The following single dose BA/BE studies were conducted:

- SP619 - the absorption, distribution, metabolism, and excretion of LCM were determined after administration of radiolabeled LCM as oral solution and solution for infusion
- SP657, SP645, and SP658 - the PK of LCM after single doses of 100, 200, or 300mg administered as an oral tablet, iv solution for infusion, —— were determined to investigate the bioequivalence of the formulations b(4)
- In SP600 - the effect of food on the PK of LCM was evaluated

PK conclusions: After administration of radiolabeled LCM as [^{14}C] oral solution, absorption was rapid and almost complete, with 94% of the administered radioactivity being recovered in urine (SP619). Bioequivalence between the tablet and the solution for infusion was shown for the iv infusions administered over 30 or 60 minutes in SP658 but not for infusion over 15 minutes (SP657). b(4)

Single Dose Proportionality Studies: SP835 (100mg, 200mg, 400mg, or 600mg LCM) and SP587 (400mg, 600mg, and 800mg)
PK conclusion: The analysis of PK parameters of LCM showed a dose-proportional increase in exposure for doses 100 through 800mg. The tmax was reached between 1 and 4 hours after dosing and the mean terminal half-life was estimated to be approximately 13 hours at all doses.

Multiple-dose Proportionality Studies P836 (100 mg, 200 mg QD for 7 days & 200 mg LMC BID for 7 days) and SP588 (300mg and 500 mg LCM BID for 13.5 days).

PK conclusions: The PK of LCM showed dose-proportional increases following both single and multiple doses up to 500 mg. The tmax was reached between 0.5 and 6 hours after dosing. The terminal half-life of LCM was approximately 13 to 14 hours. The PK characteristics did not change during multiple dosing, i.e., multiple-dose PK could be predicted from single dose data.

PK after intravenous administration- SP834 - single doses of 50mg, 100mg, 150mg, or 300mg LCM administered intravenously over 10 minutes.
PK conclusion: Cmax of LCM increased proportionally with the administered dose and the terminal half-life was estimated to be approximately 13 hours.

SP640 – thorough QT/QTc study - There were 4 treatment arms: LCM 400mg/day, LCM 800mg/day, placebo, and positive control (400mg/day moxifloxacin) in 247 subjects. Subjects had 6 days of treatment with LCM 400mg/day, LCM 800mg/day, or placebo, or 3 days of treatment with 400mg/day moxifloxacin.
PK conclusion: PK of LCM 400mg/day and LCM 800mg/day were dose-proportional and comparable to those observed in previous trials. There were no differences in PK parameters between males and females after normalization to dose and body weight, indicating no effect of gender on LCM PK parameters.
PD and PK-PD results: The difference in the maximum time-matched change from Baseline in individually corrected QT interval (QTcI) between the 400mg/day LCM group and placebo was -4.3 and between the 800mg/day LCM group and placebo was -6.3. In both cases, the upper limit of the 90% CI was below the 10ms non-inferiority margin (-0.5 and -2.5 for LCM 400mg/day and LCM 800mg/day, respectively), thereby demonstrating that there is no increase of QTcI caused by LCM.
The regression analysis showed that there is no correlation between the QTcI interval and plasma concentration of LCM. Results correlating plasma concentrations of LCM with QTcF, QTcB, and uncorrected QT were similar to those seen for QTcI.

The study will be reviewed by the QT IRT.

Abuse potential evaluation - SP903 - the abuse potential of LCM was assessed using single oral doses of LCM (200 & 800 mg) compared to the active comparator alprazolam (1.5 & 3 mg) and placebo. This study may need to be consulted to the Substance Abuse group.
PK and PD conclusions: PK of LCM was dose proportional between 200 and 800 mg and there is no clinically relevant risk of abuse for LCM.

Pharmacokinetics of LCM in special populations
Age and gender - SP620 - Healthy elderly male and female subjects and healthy young male subjects received single doses of 100mg LCM on Days 1 and 8 and 100mg LCM twice daily on Days 4 to 7

PK Conclusions: Higher LCM plasma concentrations for elderly subjects after a single dose and at steady state compared to healthy young male subjects. Higher exposure in elderly females compared to elderly male subjects. The clinical relevance of the observed differences in exposure to LCM will be a review issue.

Poor and extensive metabolizers (CYP2C19)- SP643 – The PK of LCM *was* compared after administration of 200 mg LCM given as iv solution or as oral tablet to 4 healthy Caucasian poor metabolizers (CYP2C19-genotyped) and 8 healthy Caucasian extensive metabolizers.
PK conclusion: The PK of LCM after oral or iv administration showed only slight (~10%) differences between PM and EM indicating that CYP2C19 has no relevant effect on the pharmacokinetics of LCM. There is ~3-fold increase in exposure in EMs to SPM 12809 (the major metabolite) indicating that CYP2C19 is involved in the metabolism of LCM.

Ethnic differences - SP661 - PK of LCM in was evaluated in subjects from 3 different ethnic groups (Black. Asian, White) following multiple-dose administration of 200mg LCM twice daily for 3.5 days.

PK conclusion: No relevant differences in the PK of LCM were observed between the 3 ethnic. Exposure to SPM 12809 were approximately 30% to 50% lower in Asian and Black subjects compared with White subjects.

Renal impairment - SP641 – In Part 1 of the study PK of LCM in subjects with mild to severe renal impairment was evaluated following single-dose administration of 100 mg LCM. In Part 2 of the trial evaluated the PK of LCM in subjects with end stage renal disease requiring hemodialysis under dialysis and non-dialysis conditions following single-dose administration of 100 mg LCM.

PK conclusion: Part 1 - AUC of LCM was 60% higher in subjects with severe renal impairment compared with healthy subjects. The pharmacokinetics of SPM 12809 were affected in a similar manner, but the differences were more pronounced.

Part 2 - exposure of LCM and SPM 12809 (measured as AUC(0-tz)) was decreased under a standard 4-hour dialysis by approximately 50%. Therefore, both LCM and SPM 12809 can be removed by hemodialysis.

Hepatic impairment - SP642 – The PK of LCM and its main metabolite SPM 12809 were evaluated in subjects with moderate hepatic impairment following multiple-dose administration of 100mg LCM twice daily.
PK conclusion: The plasma concentrations of LCM were approximately 50% to 60% higher in subjects with hepatic impairment compared with healthy subjects. The plasma concentration of SPM 12809 was approximately 40% to 50% lower in subjects with hepatic impairment compared with healthy subjects indicating that the liver is involved in the metabolism of LCM.

Drug-drug interaction
Digoxin interaction - SP644 - The PK of digoxin with and without coadministration of LCM was evaluated. The influence of digoxin on the PK of LCM was also assessed in a "historical comparison" with data for LCM from previous trials.
PK and PD conclusion: The PK of digoxin were not influenced by coadministration of LCM. Based on a historical comparison with PK data of LCM from previous trials, it can be concluded that coadministration of digoxin had no relevant influence on the PK of LCM.

Metformin interaction - SP660 - the possible influence of the concomitant administration of 200 mg LCM twice daily on the PK of 500 mg metformin 3 times daily and vice versa. Single-dose PK were evaluated for LCM and metformin.
PK conclusion: No PK interaction between LCM and metformin.

Valproic acid interaction - SP601 and SP602 - The possible influence of the concomitant steady-state administration of 200 mg LCM twice daily on the PK of 300 mg valproic acid twice daily and vice versa.
PK conclusion: No PK interaction between LCM and vaproic acid.

Carbamazepine interaction - SP603 and SP618- The possible influence of the concomitant steady-state administration of 200 mg LCM twice daily on the PK of 200 mg carbamazepine twice daily and vice versa.
PK conclusion: No PK interaction between LCM and carbamazepine.

Omeprazole interaction – SP683 - The possible influence of 300 mg LCM twice daily multiple-dose treatment on the PK of 40 mg omeprazole single-dose treatment and the possible influence of 40 mg omeprazole once daily multiple-dose treatment on the PK of 300 mg LCM single-dose treatment in healthy volunteers was evaluated.
PK conclusion: The administration of 300 mg LCM twice daily at steady state did not influence the PK of 40 mg omeprazole single-dose indicating that LCM does not inhibit CYP2C19. The administration of 40 mg omeprazole once daily multiple-dose treatment did not influence the PK of 300 mg LCM single-dose treatment but reduced the formation

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of SPM 12809 by approximately 60% indicating that CYP2C19 is mainly responsible for the formation of SPM 12809.

Oral contraceptive interaction – SP599 – The effect of LCM on the suppression of ovulation by an oral contraceptive containing ethinylestradiol and levonorgestrel (Microgynon®) and the effect of LCM on the PK of Microgynon®.
PK and PD conclusion: No effect of LCM on the contraceptive effect of Microgynon® was observed. Lacosamide had no effect on the PK of ethinylestradiol and levonorgestrel. A historical comparison showed that the PK of LCM were not affected by coadministration of Microgynon®.

Population PK analyses
The purpose of the population PK analyses was to describe the population PK of LCM by a population PK model and to test the influence of subject-specific factors (i.e., possible covariates) on the pharmacokinetics of LCM in healthy subjects and in the target patient populations. Population PK analyses were conducted based on LCM plasma concentration data collected in the following trials:
- SP620 and SP640 (healthy subjects)
- SP755 and SP754 (subjects with epilepsy)
- SP665, SP742, and SP743 (subjects with diabetic neuropathic pain)

Pharmacokinetics of LCM in the target populations
Plasma concentration data of LCM were obtained in the following Phase 2/3 trials in subjects with partial-onset seizures (after administration of LCM as tablet and/or iv solution for infusion) and in subjects with neuropathic pain (after administration of LCM as tablet):
- Epilepsy: SP586, SP598, SP607, SP615, SP616, SP667, SP754, SP755, SP756, SP757, and SP774
- Neuropathic pain: SP614, SP665, SP742, SP743, SP745, SP746, SP768, and SP830 (trials in subjects with diabetic neuropathic pain), SP611 (trial in subjects with —— —— neuropathic pain), and SP655 and SP690 (trials in subjects with painful postherpetic neuralgia)

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Plasma concentrations of the main metabolite SPM 12809 were determined additionally in SP655 and SP757. Summaries key PK data from these Phase 2/3 trials were submitted.

Overall conclusion from population PK analyses
- Plasma concentrations of LCM in healthy subjects and in the target populations of subjects with epilepsy or diabetic neuropathic pain were described by a 1-compartment model with first-order absorption and first-order elimination (ADVAN2) with interindividual variability on V/f and ke.
- The mean population PK parameter estimates for ke and V/f in the target populations were comparable with PK parameters determined in Phase 1 trials in healthy subjects by non-compartmental analysis and population PK analyses.
- The low IIV of LCM population PK parameters indicate that LCM plasma concentrations are highly predictable in the target populations.

• Based on the final model results, the major determinant for V/f and therefore LCM plasma concentrations was the subjects' LBW and height.
• Based on the final model results, 15% to 20% lower LCM plasma concentrations were predicted under coadministration with carbamazepine alone or in combination with 1 or 2 other AEDs in subjects with partial-onset seizures. A similar reduction was predicted under coadministration of phenobarbital or phenytoin alone, or in combination with 1 or 2 other AEDs.
• None of the other tested concomitant AEDs or AED combinations (including topiramate, lamotrigine, valproate, levetiracetam, oxcarbazepine, gabapentin, clonazepam, zonisamide) were identified as covariates on the pharmacokinetics of LCM, ie, these AEDs or AED combinations provided no clear signal of an influence on the pharmacokinetics of LCM although an influence can not be excluded.
• Overall, based on population PK results, no dose adjustment is considered necessary with regard to the tested subject-specific factors and concomitant AEDs.

PK-PD modeling
The PK-PD results support the therapeutic range of LCM doses (200 to —ng/day) that have been shown to be effective for reducing partial seizure frequency.
For the DNP indication, the PK-PD analysis —

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Comments to the Sponsor:
1. Please submit the applicable data from the following to support the population PK analyses and concentration-response relationship analyses:

- •All datasets used for model development and validation should be submitted as SAS transport files (*.xpt). A description of each data item should be provided in a Define.pdf file. Any concentrations and/or subjects that have been excluded from the analysis should be flagged and maintained in the datasets.
- •Model codes or control streams and output listings should be provided for all major model building steps, e.g., base structural model, covariates models, final model, and validation model. These files should be submitted as ASCII text files with *.txt extension (e.g.: myfile_ctl.txt, myfile_out.txt).
- •A model development decision tree and/or table which gives an overview of modeling steps.

For the population analysis reports we request that you submit, in addition to the standard model diagnostic plots, individual plots for a representative number of subjects. Each individual plot should include observed concentrations, the individual prediction line and the population prediction line. In the report, tables should include model parameter names and units. For example, oral clearance should be presented as CL/F (L/h) and not as THETA(1). Also provide in the summary of the report a description of the clinical application of modeling results.

2. Under individual subject listing for each study, the data listing dataset folder has numerous datasets. The definition of these data sets should be provided. We acknowledge

the definition of the data columns within these data sets has been provided, but description of datasets like ALCO, CAFF etc have not been provided. Under analysis dataset, the description of PC, PP and PC-E have not been given.

3. The PK-PD modeling report for epilepsy is not under the Folder 5.3.4 (reports for human PD studies). Neither is it present in the tabular listing of all studies. It was found in the Folder 5.3.5 (reports for efficacy and safety studies). Please verify that all studies/ Modeling reports submitted to the NDA are listed under the Tabular listing of studies.

Mid-Cycle Review Deliverables

- Review of:
  - Exposure response (both for desired as well as undesired effects)
  - Dose individualization
  - Needed studies of drug-drug interaction and metabolic characterization
- Provisional assessment for the following key questions:
  - Does the dose response support efficacy of the product?
  - Is the appropriate dose or dose range identified?
  - Is the proposed dose individualization scheme reasonable?
  - Are the metabolic pathways and potential for drug-drug interactions adequately characterized?
  - Were the relevant special population studies conducted?
  - Are there any "show stoppers" (i.e. issues that could preclude approval) regarding the above key components or other aspects of the application?

Recommendation: The Office of Clinical Pharmacology, Division of Clinical Pharmacology 2 has reviewed of NDA 22-253 submitted on September 28, 2007 for filing and finds it filable from clinical pharmacology perspective.

Conclusion: The application is FILABLE. Please forward the above requests to the Sponsor.

Below is the filing checklist from DNP.

b(4)

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING CHECKLIST FOR A NEW NDA/BLA

NDA Number: 22-253 **Applicant: Schwarz** **Stamp Date: 9/28/2007**

Drug Name: Lacosamide Tablets **NDA Type: Standard**

	Content Parameter	Yes	No	Comment
Criteria for Refusal to File (RTF)				
1	Has the sponsor submitted bioequivalence data comparing to-be-marketed product(s) and those used in the pivotal clinical trials?	X		Biowaiver requested and can be granted based on BCS I classification
2	Has the sponsor provided metabolism and drug-drug interaction information?	X		
Criteria for Assessing Quality of an NDA				
	Data			
3	Are the data sets, as requested at the earlier meeting (e.g.: Pre-NDA meeting), submitted in the appropriate format (e.g. CDISC)?		X	Definition of datasets for Clinical Pharmacology and Biopharmaceutics studies not provided, but definition of columns within the dataset has been provided. Population PK and PK-PD dataset along with NONMEM control stream and output listing is not provided.
4	If applicable, are the pharmacogenomic data sets submitted in the appropriate format?	NA		
	Studies and Analyses			
5	Has the Sponsor made an appropriate attempt to determine the reasonable dose individualization strategy for this product (i.e., appropriately designed and analyzed dose-ranging or pivotal studies)?	X		
6	Did the sponsor follow the scientific advice provided regarding matters related to dose selection?	X		
7	Are the appropriate exposure-response (for desired and undesired effects) analyses conducted and submitted in a format as described in the Exposure-Response guidance?		X	No datasets provided.
8	Is there an adequate attempt by the sponsor to use exposure-response relationships in order to assess the need for dose adjustments for intrinsic/extrinsic factors that might affect the pharmacokinetic or pharmacodynamics?	X		
9	Are the pediatric exclusivity studies adequately designed to demonstrate effectiveness, if the drug is indeed effective?	NA		PK information in adolescents is obtained from the three Phase 3 studies.
10	Did the sponsor submit all the pediatric exclusivity data, as described in the WR?	NA		No written request given to the sponsor

11	Is the appropriate pharmacokinetic information submitted?	X		
12	Is there adequate information on the pharmacokinetics and exposure-response in the clinical pharmacology section of the label?	X		
	General			
13	On its face, is the clinical pharmacology and biopharmaceutical section of the NDA organized in a manner to allow substantive review to begin?	X		
14	Is the clinical pharmacology and biopharmaceutical section of the NDA indexed and paginated in a manner to allow substantive review to begin?	X		
15	On its face, is the clinical pharmacology and biopharmaceutical section of the NDA legible so that a substantive review can begin?	X		
16	Are the clinical pharmacology and biopharmaceutical studies of appropriate design and breadth of investigation to meet basic requirements for approvability of this product?	X		
17	Was the translation from another language important or needed for publication?	NA		

Any Additional Comments:

Comments to the sponsor:

- Under individual subject listing for each study, the data listing dataset folder has numerous datasets. The definition of these data sets should be provided. We acknowledge the definition of the data columns within these data sets has been provided, but description of datasets like ALCO, CAFF etc have not been provided. Under analysis dataset, the description of PC, PP and PC-E have not been given.

- The PK-PD modeling report for epilepsy is not under the Folder 5.3.4 (reports for human PD studies). Neither is it present in the tabular listing of all studies. It was found in the Folder 5.3.5 (reports for efficacy and safety studies).

Reviewing Pharmacologist Date

Team Leader/Supervisor Date

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

/s/

Emmanuel Fadiran
11/28/2007 12:32:25 PM
BIOPHARMACEUTICS

Suresh Doddapaneni
11/28/2007 08:36:14 PM
BIOPHARMACEUTICS

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING CHECKLIST FOR A NEW NDA/BLA

NDA Number: 22-253 **Applicant: Schwarz** **Stamp Date: 9/28/2007**

Drug Name: Lacosamide Tablets **NDA Type: Standard**

	Content Parameter	Yes	No	Comment
Criteria for Refusal to File (RTF)				
1	Has the sponsor submitted bioequivalence data comparing to-be-marketed product(s) and those used in the pivotal clinical trials?	X		Biowaiver requested and can be granted based on BCS I classification
2	Has the sponsor provided metabolism and drug-drug interaction information?	X		
Criteria for Assessing Quality of an NDA				
	Data			
3	Are the data sets, as requested at the earlier meeting (e.g.: Pre-NDA meeting), submitted in the appropriate format (e.g. CDISC)?		X	Definition of datasets for Clinical Pharmacology and Biopharmaceutics studies not provided, but definition of columns within the dataset has been provided. Population PK and PK-PD dataset along with NONMEM control stream and output listing is not provided.
4	If applicable, are the pharmacogenomic data sets submitted in the appropriate format?	NA		
	Studies and Analyses			
5	Has the Sponsor made an appropriate attempt to determine the reasonable dose individualization strategy for this product (i.e., appropriately designed and analyzed dose-ranging or pivotal studies)?	X		
6	Did the sponsor follow the scientific advice provided regarding matters related to dose selection?	X		
7	Are the appropriate exposure-response (for desired and undesired effects) analyses conducted and submitted in a format as described in the Exposure-Response guidance?	X		No datasets provided.
8	Is there an adequate attempt by the sponsor to use exposure-response relationships in order to assess the need for dose adjustments for intrinsic/extrinsic factors that might affect the pharmacokinetic or pharmacodynamics?	X		
9	Are the pediatric exclusivity studies adequately designed to demonstrate effectiveness, if the drug is indeed effective?	NA		PK information in adolescents is obtained from the three Phase 3 studies (Proposed label for ≥16 years

10	Did the sponsor submit all the pediatric exclusivity data, as described in the WR?	NA		No written request given to the sponsor
11	Is the appropriate pharmacokinetic information submitted?	X		
12	Is there adequate information on the pharmacokinetics and exposure-response in the clinical pharmacology section of the label?	X		
	General			
13	On its face, is the clinical pharmacology and biopharmaceutical section of the NDA organized in a manner to allow substantive review to begin?	X		
14	Is the clinical pharmacology and biopharmaceutical section of the NDA indexed and paginated in a manner to allow substantive review to begin?	X		
15	On its face, is the clinical pharmacology and biopharmaceutical section of the NDA legible so that a substantive review can begin?	X		
16	Are the clinical pharmacology and biopharmaceutical studies of appropriate design and breadth of investigation to meet basic requirements for approvability of this product?	X		
17	Was the translation from another language important or needed for publication?	NA		

Any Additional Comments:

Comments to the sponsor:

- Under individual subject listing for each study, the data listing dataset folder has numerous datasets. The definition of these data sets should be provided. We acknowledge the definition of the data columns within these data sets has been provided, but description of datasets like ALCO, CAFF etc have not been provided. Under analysis dataset, the description of PC, PP and PC-E have not been given.

- The PK-PD modeling report for epilepsy is not under the Folder 5.3.4 (reports for human PD studies). Neither is it present in the tabular listing of all studies. It was found in the Folder 5.3.5 (reports for efficacy and safety studies). Please verify that all studies/ Modeling reports submitted to the NDA are listed under the Tabular listing of studies.

- Please submit the applicable data from the following to support ALL population PK analyses and concentration-response relationship analyses:
    - All datasets used for model development and validation should be submitted as SAS transport files (*.xpt). A description of each data item should be provided in a Define.pdf file. Any concentrations and/or subjects that have been excluded from the analysis should be flagged and

maintained in the datasets.

- Model codes or control streams and output listings should be provided for all major model building steps, e.g., base structural model, covariates models, final model, and validation model. These files should be submitted as ASCII text files with *.txt extension (e.g.: myfile_ctl.txt, myfile_out.txt).
- A model development decision tree and/or table which gives an overview of modeling steps.
- For the population analysis reports we request that you submit, in addition to the standard model diagnostic plots, individual plots for a representative number of subjects. Each individual plot should include observed concentrations, the individual prediction line and the population prediction line. In the report, tables should include model parameter names and units. For example, oral clearance should be presented as CL/F (L/h) and not as THETA(1). Also provide in the summary of the report a description of the clinical application of modeling results.

Reviewing Pharmacologist Date

Team Leader/Supervisor Date

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

/s/

Veneeta Tandon
11/20/2007 01:34:10 PM
BIOPHARMACEUTICS

Ramana S. Uppoor
11/20/2007 01:53:29 PM
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