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

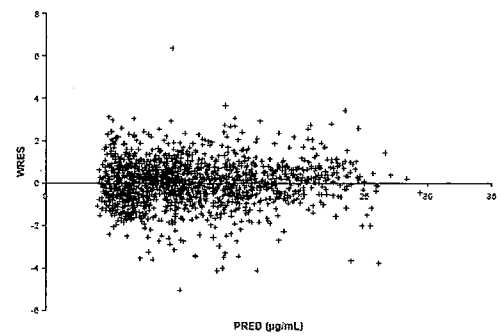
b(4)

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

(A)

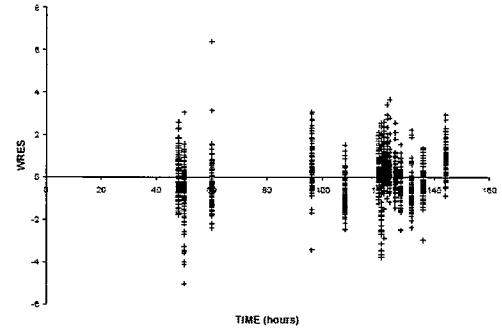
Data source: Appendix 6
Dotted line=linear regression (incl. equation and R-squared), line of identity (solid) is included as a reference.

(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

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