Population Pharmacokinetics of the new Antiepileptic Drug Lacosamide in Healthy Subjects with Different Age and Gender

SCHWARZ PHARMA

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Introduction

Lacosamide (R-2-acetamido-N-benzyl-3-methoxypropionamide, formerly known as harcoseride) is a new drug under clinical development by Schwarz Biosciences for the treatment of epilepsy and neuropathic pain. About 40 % of the drug is renally excreted as unchanged compound. Major metabolic pathway is demethylation, the inactive O-desmethyl-metabolite is excreted with the urine and represents about 30 % of the dose.

Objectives

- To characterize population pharmacokinetics of unchanged lacosamide in healthy elderly males and females (>65 years) in comparison to young healthy males (18–45 years)
- To identify possible covariates that may have an influence on the pharmacokinetics (PK) of lacosamide in the trial population of healthy subjects to explain inter-individual variability

Study Design

- Double-blind, placebo-controlled, parallel group trial
- 47 subjects in 3 groups:
  - 15 elderly males (EM): 11 verum, 4 placebo
  - 16 elderly females (EF): 12 verum, 4 placebo
  - 16 young males (YM): 12 verum, 4 placebo
- Day 1, 8: 100 mg lacosamide oral single dose administration
- Day 4, 5, 6, 7: 100 mg lacosamide bid oral administration
- 33 blood samples were taken from Day 1 to Day 11 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, 156 hours following first dose on Day 1
  - 0 (pre-dose), 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 24, 36, 48 and 72 hours following last dose on morning of Day 8

Tested Covariates

- Age
- Sex
- Body weight (BW)
- Height
- Body Mass Index (BMI)
- Creatinine Clearance (CL_{crea}): Calculated using Cockcroft-Gault equation based on serum creatinine, age, weight and sex

Pharmacokinetic Methods

- Software: NONMEM Version 5 in combination with PDxPop Version 1.1
- Subroutine ADVAN2: One-compartment model with first-order absorption and elimination with the parameters:
  - k_a: rate constant of absorption
  - k_e: rate constant of elimination
  - V/f: apparent volume of distribution

Bioanalytical Method

- Highly sensitive and selective LC-MS/MS method for lacosamide with deuterated internal standard (solid-phase extraction)
- Calibration range: 0.01–10 µg/mL

Results

Demographic Parameters for each Group (Arithmetic Mean ± SD)

Group*	N	Age [years]	Height [cm]	Weight [kg]	BMI [kg/m²]
EM	15	71.9 ± 6.4	173.6 ± 8.2	80.1 ± 11.6	26.5 ± 2.6
EF	16	68.9 ± 3.9	161.7 ± 6.4	66.1 ± 10.3	25.2 ± 2.9
YM	16	36.0 ± 6.7	177.6 ± 8.0	77.7 ± 11.2	24.6 ± 2.6

*EM = Elderly males, EF = Elderly females, YM = Young males

Base Model Development

The objectives of the base model development were:

- To identify the most suitable error model for the description of residual random variability
- To identify the most suitable model for the description of inter-individual variability (IIV) of population PK parameters

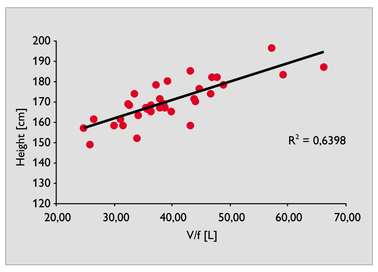
The following model was chosen as base model for the evaluation of possible covariates during the final model development :

- Combined residual random error model (proportional and additive component)
- Exponential inclusion of inter-individual variability on k_e, k_a and V/f
- No lag-time

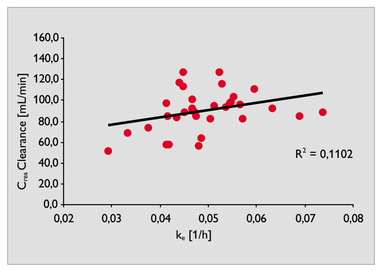
Final Model Development

Diagnostic Plots Covariates vs. Individual PK Parameters

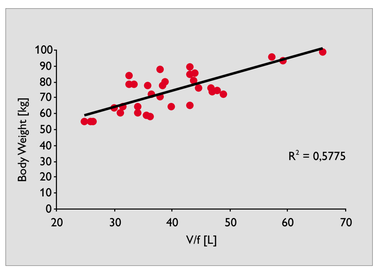
V/f vs Height



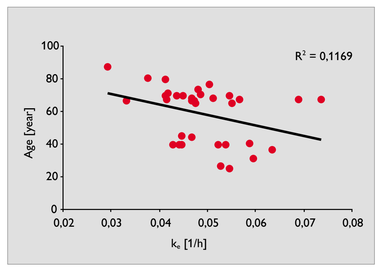
k_e vs CLcrea



V/f vs Weight



k_e vs Age



Statistical Testing of Covariates

The following table summarizes important steps of covariate testing on the base model (without covariates) during final model development:

Description of covariates	OBF	IIV of k_e [%]	IIV of k_a [%]	IIV of V/f [%]	Residual Error σ (Prop./Add.)
Base Model	–1660.2	19.2	112	21.4	7.9%/0.06
Body weight on V/f	–1415.1	21.6	123	40.9	7.6%/0.08
Height on V/f	–1718.7	18.6	117	11.9	7.9%/0.06
Sex on V/f	–1701.7	19.4	115	14.0	7.9%/0.06
Age on k_e	–1222.2	35.4	119	25.0	7.4%/0.13
CL_{crea} on k_e	–1720.1	16.4	112	21.5	8.2%/0.06
Height + Sex on V/f CL_{crea} on k_e	–1783.0	15.9	117	10.3	8.2%/0.06
Height + Sex on V/f CL_{crea} + Sex on k_e	–1805.8	14.7	117	10.2	8.2%/0.05

OBF = Objective Function, IIV = inter-individual variability

Final Model

The following model was chosen as final model with the following characteristics:

- 1-comp.-model with first-order absorption and elimination without lag-time (ADVAN2, FOCE)
- Height and sex as covariates on V/f
- CL_{crea} and sex as covariates on k_e
- Low inter-individual variability (<15 %) for V/f and k_e
- Low residual variability: 8.2 % (proportional error), 0.05 µg/mL (additive error)
- Predominantly high precision of final estimates (RSE<25 %)

Final Population PK Parameter Estimates

Parameter	Final Estimate [%RSE]	IIV [%RSE]
V/f [L]	42.4 + θ 4 * (Height–169) + θ 5 * Gender [2.7]	10.2 % [27.9]
k_e [h^{-1}]	0.0225 + θ 6 * CL_{crea} + θ 7 * Gender [17.2]	14.7 % [17.5]
k_a [h^{-1}]	4.20 [12.2]	117 % [29.1]
θ 4	0.415 [23.9]	–
θ 5	–6.90 [25.5]	–
θ 6	0.000245 [17.4]	–
θ 7	0.00705 [36.9]	–
Residual Error σ	8.15%/0.0532 µg/mL [8.58, 35.1]	–

*θ = mean parameter (THETA), IIV = inter-individual variability, %RSE = relative standard error in percent

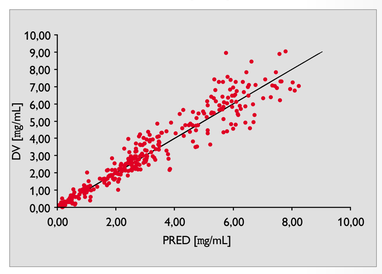
The following population means were estimated for a subject with a median height of 1.69 m and a median CL_{crea} of 89 mL/min:

	Males	Females [change]*
V/f [L]	42.4	35.5 [–16 %]
$t_{1/2}$ [h]	15.6	13.5 [–14 %]
k_a [h^{-1}]	4.20	4.20

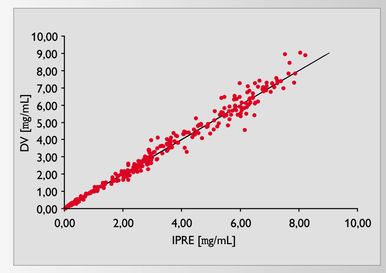
*decrease compared to males

Goodness of Fit of the Final Model

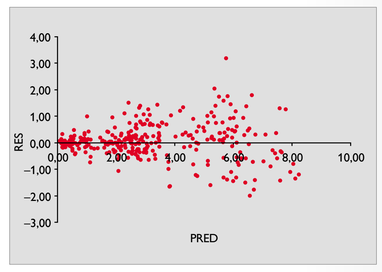
Population Predictions (PRED) vs. Measured Conc. (DV)



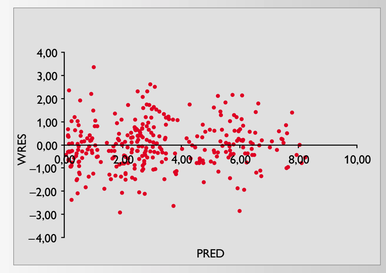
Individual Predictions (IPRE) vs. Measured Conc. (DV)



Population Predictions (PRED) vs. Residuals (RES)

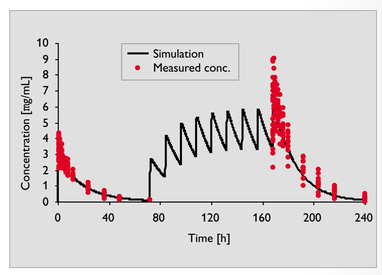


Population Predictions (PRED) vs. Weighted Residuals (WRES)

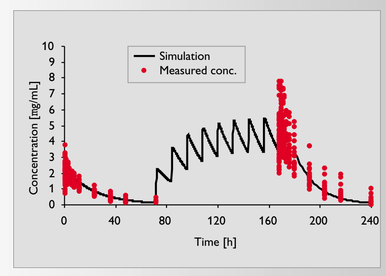


Simulation Based on Final Population Estimates:

Females



Males



Discussion

- A major part of inter-individual variability of V/f (~10 %) could be explained by differences in height and sex:
  - Observed higher plasma concentrations of lacosamide in females are the result of the smaller V/f in this subpopulation.
  - As lacosamide is highly soluble in water and mainly distributes in extracellular fluid, changes in height are linked with changes in V/f.
- A smaller part of inter-individual variability of k_e (~ 5 %) could be explained by differences in CL_{crea} and sex.

Conclusion

- **An adequate population PK model was developed for the description of plasma concentrations of lacosamide in healthy subjects.**
- **Inter-individual variability of V/f and k_e can be explained to a large extent by differences in height, sex and CL_{crea}.**
- **Exposure of lacosamide is highly predictable in individuals.**
- **The current population PK model will be used as basis for PopPK evaluations in Phase 2/3 to verify the results in the target population.**