# Supplemental Information

Article: *Impact of perampanel on pharmacokinetics of concomitant antiepileptics in patients with partial-onset seizures: pooled analysis of clinical trials.*

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**A. Compiling datasets for concomitant AED analyses**

A NONMEM event file was created by juxtaposing AED dosing and sampling events, demographic variables, laboratory variables, study treatments (placebo or perampanel doses), perampanel observed concentrations (mean of 2 samples on a single day). Subjects treated with discontinued AED(s) and subjects with inconsistent AED information, or not in the PK/PD population, were removed.

## B. Model details for each concomitant AED

Carbamazepine

The variance of the residual error was estimated with a combined proportional error model. Goodness of fit (GOF) plots of the final model show that the population and individual predicted concentrations versus the observed concentrations on the linear or logarithmic scales did not show large systematic bias in the predictions.

*Supplemental Table S-1: Population parameter estimates for carbamazepine final PK model*

| **Fixed effects** | **Final estimate** | **SEE %** | **95% CI** | **%CV** |
|---|---|---|---|---|
| Carbamazepine basal clearance (L/h) | 0.375 | 18.2 | 0.241; 0.509 | – |
| Carbamazepine dose effect | 0.00347 | 4.2 | 0.003; 0.004 | – |
| Valproic acid effect | 0.125 | 37.8 | 0.032; 0.218 | – |
| Perampanel dose effect | 0.00357 | 49.9 | 0.0001; 0.0071 | – |
| **Between-subject variability in clearance** | | | | |
| IIV | 0.0512 | 8.9 | -- | 22.6 |
| IOV | 0.0246 | 8.8 | -- | 15.7 |
| **Residual error model** | | | | |
| proportional | 0.0167 | 10.5 | -- | 12.9 |

CI: confidence interval; CV: coefficient of variation; IIV: inter-individual variability; IOV: inter-occasion variability; SEE: standard error of the estimate, %.

Clobazam

GOF plots showed that the population and individual predicted concentrations versus the observed concentrations on the linear and logarithmic scale did not show systematic bias in the predictions.

*Supplemental Table S-2: Population parameter estimates for clobazam final PK model*

| **Fixed effects** | **Final estimate** | **SEE %** | **95% CI** | **%CV** |
|---|---|---|---|---|
| Clobazam basal clearance (L/h) | 4.76 | 18 | 3.014; 6.479 | – |
| Sex effect | −0.387 | 16 | −0.507; −0.267 | – |
| Weight effect | −0.312 | 25 | −0.466; −0.158 | – |
| Phenytoin effect | 0.545 | 31 | 0.212; 0.878 | – |
| Perampanel concentration effect | 0.0000678 | 32 | 0.0000249; 0.0001107 | |
| **Between-subject variability in clearance** | | | | |
| IIV | 0.497 | 23 | -- | 70.5 |
| IOV | 0.0258 | 21 | -- | 16.1 |
| **Residual error model** | | | | |
| proportional | 0.059 | 17 | -- | 5.9 |

CI: confidence interval; CV: coefficient of variation; IIV: inter-individual variability; IOV: inter-occasion variability; SEE: standard error of the estimate, %.

Clonazepam

GOF plots showed that the population and individual predicted concentrations versus the observed concentrations on the linear and logarithmic scale did not show any systematic bias in the predictions.

*Supplemental Table S-3: Population parameter estimates for base/final clonazepam PK model*

| **Fixed effects** | **Final estimate** | **SEE %** | **95% CI** | **%CV** |
|---|---|---|---|---|
| Clonazepam basal clearance (L/h) | 2.53 | 18 | 3.041; 6.479 | – |
| Effect of phenytoin | 1.89 | −16 | −0.507; −0.267 | – |
| Effect of valproic acid | 0.785 | −25 | −0.466; −0.158 | – |
| Effect of clobazam | 1.01 | 31 | 0.212; 0.878 | – |
| **Between-subject variability in clearance** | | | | |
| IIV | 0.388 | 23 | – | 70.5 |
| IOV | 0.0513 | 21 | – | 16.1 |
| **Residual error model** | | | | |
| proportional | 0.0171 | 17 | – | 5.9 |

CI: confidence interval; CV: coefficient of variation; IIV: inter-individual variability; IOV: inter-occasion variability; SEE: standard error of the estimate, %.

Lamotrigine

The variance of the residual error was estimated with a combined proportional and additive error model. GOF plots showed that the population and individual predicted concentrations versus the observed concentrations on the linear and logarithmic scales did not show systematic bias in the predictions.

*Supplemental Table S-4: Population parameter estimates for lamotrigine final PK model*

| **Fixed effects** | **Final estimate** | **SEE %** | **95% CI** | **%CV** |
|---|---|---|---|---|
| Lamotrigine basal clearance (L/h) | 1.18 | 6 | 1.043; 1.317 | – |
| Effect of carbamazepine | 0.584 | 27 | 0.28; 0.888 | – |
| Effect of phenobarbital | 0.742 | 35 | 0.228; 1.256 | – |
| Effect of valproic acid | −0.51 | 14 | −0.648; −0.372 | – |
| Effect of perampanel dose: slope log(dose) | 0.037 | 26 | 0.018; 0.056 | |
| **Between-subject variability in clearance** | | | | |
| IIV | 0.249 | 7 | – | 49.9 |
| IOV | 0.0296 | 13 | – | 17.2 |
| **Residual error model** | | | | |
| proportional | 0.0193 | 16 | – | 1.9 |

CI: confidence interval; CV: coefficient of variation; IIV: inter-individual variability; IOV: inter-occasion variability; SEE: standard error of the estimate, %.

Levetiracetam

The variance of the residual error was estimated with a combined proportional and additive error model. GOF plots showed that the population and individual predicted concentrations versus the observed concentrations on the logarithmic scale did not show any systematic bias in the predictions.

*Supplemental Table S-5: Population parameter estimates for base/final levetiracetam PK model*

| **Fixed effects** | **Final estimate** | **SEE %** | **95% CI** | **%CV** |
|---|---|---|---|---|
| Levetiracetam basal clearance (L/h) | 2.28 | 5 | 2.043; 2.517 | – |
| Sex effect | −0.244 | 23 | −0.356; −0.132 | – |
| Weight effect | 0.389 | 43 | 0.062; 0.716 | – |
| Phenytoin effect | −0.252 | 49 | −0.495; −0.009 | |
| Valproic acid effect | −0.154 | 39 | −0.273; −0.035 | – |
| **Between-subject variability in clearance** | | | | |
| IIV | 0.23 | 11 | – | 48.0 |
| IOV | 0.034 | 19 | – | 18.4 |
| **Residual error model** | | | | |
| proportional | 0.0717 | 11 | – | 7.2 |

CI: confidence interval; CV: coefficient of variation; IIV: inter-individual variability; IOV: inter-occasion variability; SEE: standard error of the estimate, %.

Oxcarbazepine

The variance of the residual error was estimated with a combined proportional and additive error model. GOF plots showed biased individual predicted concentrations versus the observed concentrations, with significant over-prediction of low concentrations, also seen on the weighted residuals plot.

*Supplemental Table S-6: Population parameter estimates for final oxcarbazepine PK model*

| **Fixed effects** | **Final estimate** | **SEE %** | **95% CI** | **%CV** |
|---|---|---|---|---|
| Oxcarbazepine basal clearance (L/h) | 63.4 | 8 | 53.953; 72.847 | – |
| Sex effect | −0.263 | −29 | −0.412; −0.114 | – |
| Phenytoin effect | 0.823 | 33 | 0.284; 1.362 | |
| Perampanel effect | −0.261 | −26 | −0.392; −0.13 | – |
| **Between-subject variability in clearance** | | | | |
| IIV | 0.305 | 13 | – | 55.2 |
| IOV | 0.195 | 13 | – | 44.2 |
| **Residual error model** | | | | |
| proportional | 0.407 | 11 | – | 40.7 |

CI: confidence interval; CV: coefficient of variation; IIV: inter-individual variability; IOV: inter-occasion variability; SEE: standard error of the estimate, %.

Phenobarbital

The variance of the residual error was estimated with a combined proportional and additive error model. GOF plots showed no systematic bias in the predictions.

*Supplemental Table S-7: Population parameter estimates for base/final phenobarbital PK model*

| **Fixed effects** | **Final estimate** | **SEE %** | **95% CI** | **%CV** |
|---|---|---|---|---|
| Phenobarbital basal clearance (L/h) | 0.243 | 9 | 0.202; 0.284 | – |
| Effect of liver function enzymes[a] | 0.24 | 28 | 0.108; 0.372 | – |
| Lamotrigine effect | −0.24 | 42 | −0.436; −0.044 | |
| Oxcarbazepine effect | −0.325 | 29 | −0.51; −0.14 | – |
| **Between-subject variability in clearance** | | | | |
| IIV | 0.281 | 32 | – | 53.0 |
| IOV | 0.0189 | 28 | – | 13.7 |
| **Residual error model** | | | | |
| proportional | 0.0112 | 25 | – | 1.1 |

CI: confidence interval; CV: coefficient of variation; IIV: inter-individual variability; IOV: inter-occasion variability; SEE: standard error of the estimate, %.
[a]Effect of liver function enzymes: aspartate aminotransferase or alanine aminotransferase greater than 2-times the upper limit of normal.

Phenytoin

The variance of the residual error was estimated with a combined proportional and additive error model. GOF plots showed no systematic bias in the predictions.

*Supplemental Table S-8: Population parameter estimates for base/final phenytoin PK model*

| **Fixed effects** | **Final estimate** | **SEE %** | **95% CI** | **%CV** |
|---|---|---|---|---|
| Phenytoin clearance (L/h) | 0.129 | 8 | 0.108; 0.15 | – |
| Oxcarbazepine effect | 0.406 | 50 | 0.008; 0.804 | – |
| Zonisamide effect | 0.524 | 39 | 0.124; 0.924 | – |
| **Between-subject variability in clearance** | | | | |
| IIV | 0.393 | 16 | – | 62.7 |
| IOV | 0.0518 | 19 | – | 22.8 |
| **Residual error model** | | | | |
| proportional | 0.0159 | 18 | – | 1.6 |

CI: confidence interval; CV: coefficient of variation; IIV: inter-individual variability; IOV: inter-occasion variability; SEE: standard error of the estimate, %.

Topiramate

The variance of the residual error was estimated with a combined proportional and additive error model. GOF plots showed that the population and individual predicted concentrations versus the observed concentrations on the linear or logarithmic scale did not show any systematic bias in the predictions.

*Supplemental Table S-9: Population parameter estimates for base/final topiramate PK model*

| **Fixed effects** | **Final estimate** | **SEE %** | **95% CI** | **%CV** |
|---|---|---|---|---|
| Topiramate basal clearance (L/h) | 0.953 | 4 | 0.885; 1.021 | – |
| Effect of weight | 0.878 | 21 | 0.519; 1.237 | – |
| Phenytoin effect | 0.714 | 37 | 0.197; 1.231 | |
| Zonisamide effect | 1.12 | 33 | 0.403, 1.837 | – |
| **Between-subject variability in clearance** | | | | |
| IIV | 0.212 | 11 | – | 46.0 |
| IOV | 0.0292 | 13 | – | 17.1 |
| **Residual error model** | | | | |
| proportional | 0.0278 | 14 | – | 2.8 |

CI: confidence interval; CV: coefficient of variation; IIV: inter-individual variability; IOV: inter-occasion variability; SEE: standard error of the estimate, %.

Valproate

The variance of the residual error was estimated with a combined proportional and additive error model. GOF plots showed that the population and individual predicted concentrations versus the observed concentrations on the logarithmic scale did not show any systematic bias in the predictions.

*Supplemental Table S-10: Population parameter estimates for final valproic acid PK model*

| **Fixed effects** | **Final estimate** | **SEE %** | **95% CI** | **%CV** |
|---|---|---|---|---|
| Valproic acid basal clearance (L/h) | 0.401 | 3 | 0.374; 0.428 | – |
| Weight effect | 0.490 | 34 | 0.161; 0.819 | – |
| Effect of perampanel dose | 0.00761 | 41 | 0.002; 0.014 | – |
| **Between-subject variability in clearance** | | | | |
| IIV | 0.316 | 8 | – | 56.2 |
| IOV | 0.0308 | 11 | – | 17.5 |
| **Residual error model** | | | | |
| proportional | 0.0259 | 12 | – | 2.6 |

CI: confidence interval; CV: coefficient of variation; IIV: inter-individual variability; IOV: inter-occasion variability; SEE: standard error of the estimate, %.

Zonisamide

The variance of the residual error was estimated with a combined proportional and additive error model. GOF plots showed that the population and individual predicted concentrations versus the observed concentrations on the logarithmic scale did not show any systematic bias in the predictions.

*Supplemental Table S-11: Population parameter estimates for final zonisamide PK model*

| **Fixed effects** | **Final estimate** | **SEE %** | **95% CI** | **%CV** |
|---|---|---|---|---|
| Zonisamide basal clearance (L/h) | 0.558 | 6 | 0.4921; 0.6219 | – |
| Phenytoin effect | 0.581 | 45 | 0.066; 1.096 | – |
| Phenobarbital effect | 0.491 | 34 | 0.16; 0.822 | |
| Clobazam effect | −0.334 | 33 | −0.55; −0.118 | – |
| **Between-subject variability in clearance** | | | | |
| IIV | 0.235 | 14 | – | 48.5 |
| IOV | 0.0216 | 22 | – | 14.7 |
| **Residual error model** | | | | |
| proportional | 0.0141 | 17 | – | 11.9 |

CI: confidence interval; CV: coefficient of variation; IIV: inter-individual variability; IOV: inter-occasion variability; SEE: standard error of the estimate, %.