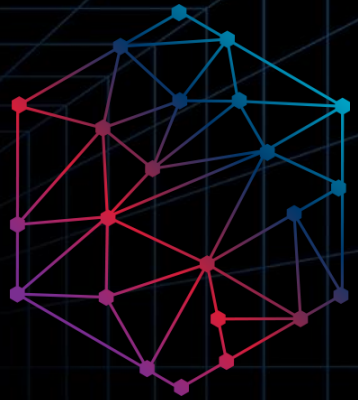
Model-Informed Drug Development

# MIDD+

2021 Virtual Conference



# Population Pharmacokinetic Evaluation and Missed-Dose Simulations for Eslicarbazepine Acetate Monotherapy in Patients With Partial-Onset Seizures

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# The Issue: Adherence to Dosing

- Adherence to a prescribed AED regimen is an important issue in the control of seizures.[1,2]
- The reported magnitude of nonadherence has ranged from 26% in the United States to 67% in Nigeria.[3,4]

# Repercussions of non-Adherence

- Risk of seizure requiring hospital or emergency admission was 21% higher in nonadherent patients when compared to adherent patients.[2]
- Inappropriate resumption of dosing may also result in higher than necessary drug concentrations and is, thus, a potential concern for toxicity.[1,5]

# Methods to Improve the Situation

- Once daily dosing typically results in improved adherence as compared to more frequent dosing[6] ; although delayed and missed doses still occur.
- Use of pharmacokinetic (PK) modeling and simulation can be used to understand the impact of delayed or missed doses on the plasma concentration profile and prospectively develop recommendations for patients and clinicians to appropriately resume dosing.[1,2,5]
- Exploratory: Understand the CSF concentration-time profile.

# Data for the Previous PK Model

- 10 Phase 1 studies and 2 Phase 3 studies of eslicarbazepine (ESL) acetate monotherapy[7]
  - 493 subjects
  - 3,869 concentrations

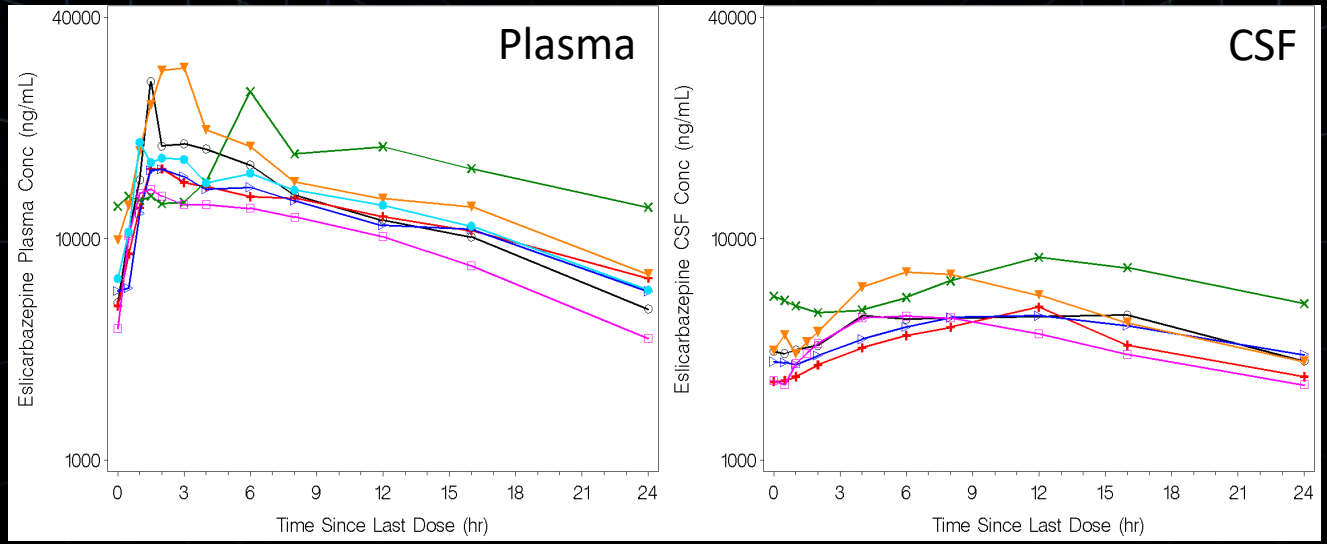
# Previous PK Model

- 1 compartment; first-order absorption & elimination
  - Phase 1: Exponential IIV in Ka, CL/F and Vc/F with additive plus constant coefficient of variation RV (ACCV).
  - Phase 3: Exponential IIV in CL/F and a constant coefficient of variation RV (CCV).
  - CL/F and V/F: Functions of weight and sex (females lower)

# Exploratory CSF Data

- 1 Phase 1 open-label multiple dose study[8]
  - Healthy adult subjects (M & F)
    - Plasma (n=7) and CSF (n=6)
  - Samples: included a profile collected from predose to 24 hours postdose
  - Unethical to collect CSF in larger numbers

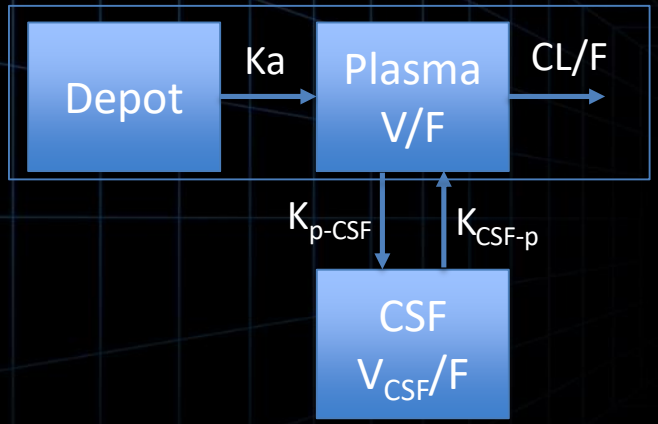
# Observed Plasma/CSF




72 plasma and 60 CSF concentrations

# Exploratory CSF Model

## Model Diagram



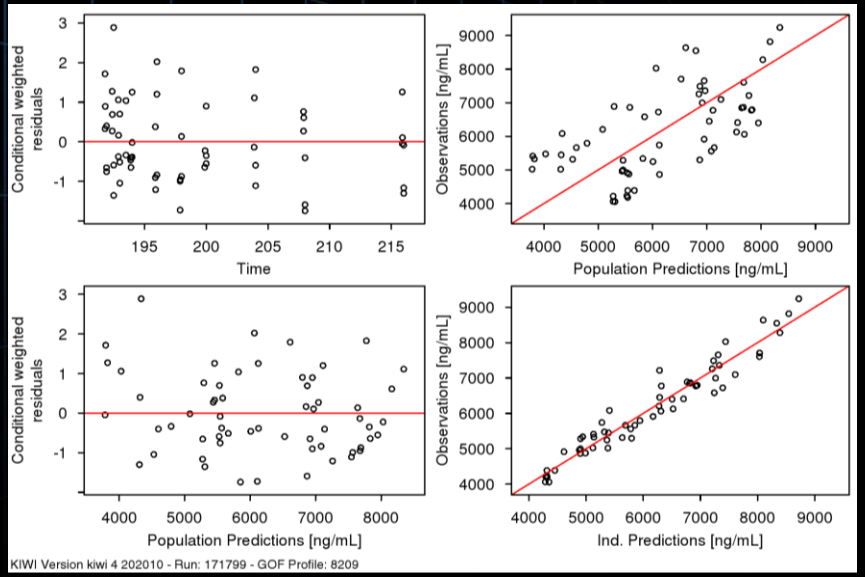

- PK: Fixed Bayesian Parameter Estimates
- 6 subjects and exploratory
- Accepted poorly estimated parameters (50% < %RSE < 100%)

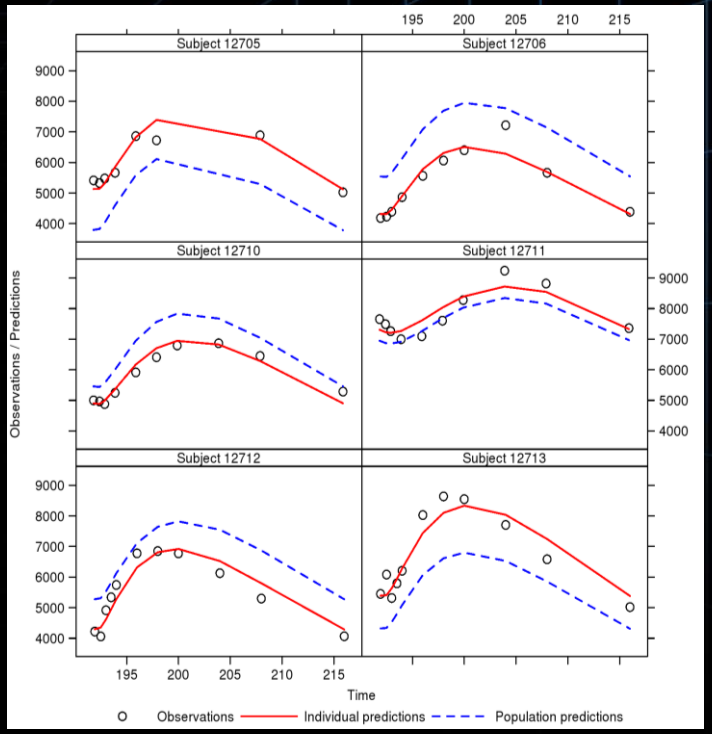
## Parameter Estimates

| Parameter Name | Parameter Estimate (%RSE) | IIV/RV Estimate %CCV (%RSE) |
|---|---|---|
| $K_{p\text{-}CSF}$ (1/h) | 0.0186 (91.4%) | Not Estimated |
| $K_{CSF\text{-}p}$ (1/h) | 0.145 (15.2%) | 19.3% (67.3%) |
| $V_{CSF}/F$ (L) | 16.9 (81.2%) | 14.1% (77%) |
| Residual Variability | 0.00308 (18.9%) | 5.55% |

# Exploratory CSF Model Fit

## Goodness-of-Fit Plots



# Simulation Target Range

- The safe and efficacious targeted concentration range:
  - estimated based on model predicted Cmin and Cmax values for patients from monotherapy phase 3 studies
  - Lower Limit (efficacy): Mean model predicted Cmin associated with patients that exited the studies prior to Day 109
  - Upper Limit (safety): 90th percentile of the PK model-predicted Cmax for patients taking 1600 mg ESL (maximum approved dose)
  - Window: 12,619 ng/mL to 43,430 ng/mL

# Secondary Simulation Target Range

- Based on efficacy[9]
- Cmin associated with a 90% probability of a patient remaining in the studies to day 109
  - 1 AED at baseline: 17,785 ng/mL
  - 2 AEDs at baseline: 27,485 ng/mL

# Simulation Population & Dosing

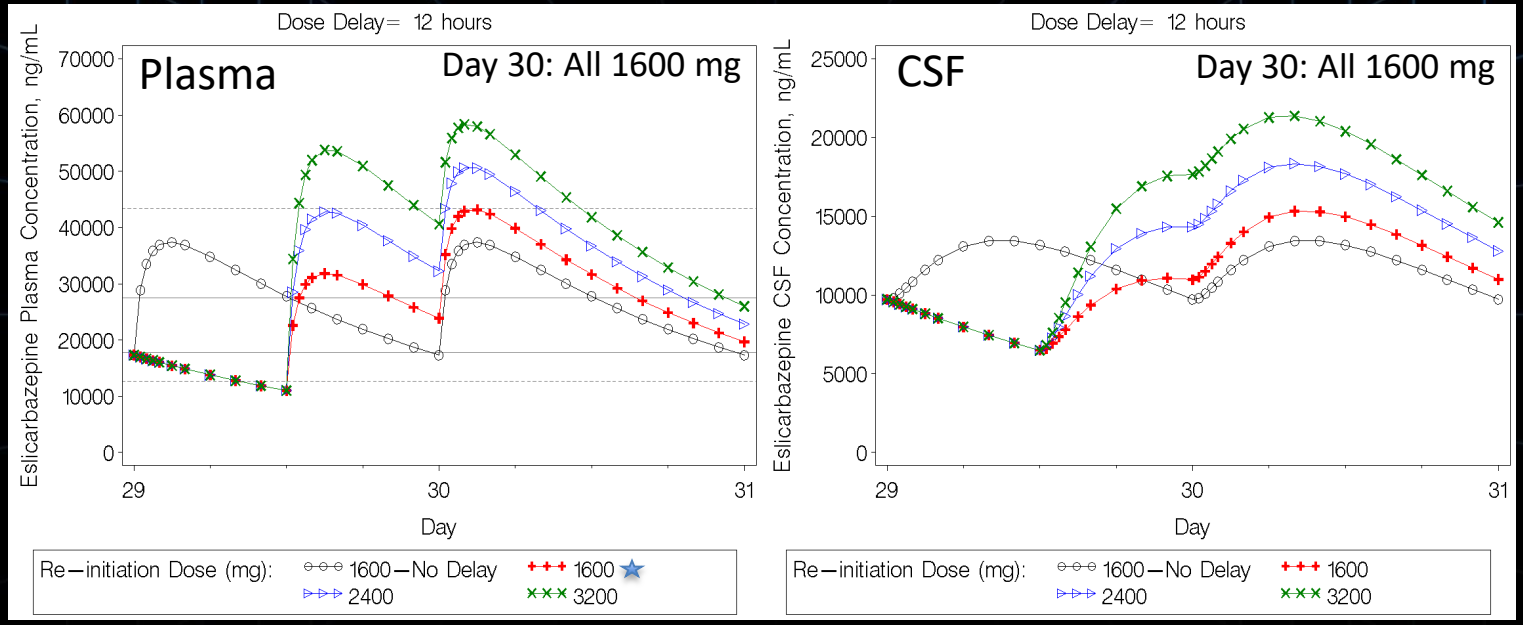
- 1200 pairs of weight and sex randomly sampled with replacement from the Phase 3 studies (302 patients) included in the previously developed PK model.
- Virtual patients were administered ESL QD:
  - 600 mg QD for 7 days,
  - then 1200 mg QD for 7 days,
  - then 1600 mg QD for 14 days (highest maintenance dose approved for ESL monotherapy), and
  - then delayed and missed doses were simulated for Days 29, 30, and 31.
- Dose of 1600 mg chosen because risk of excessively high plasma concentrations on resumption of dosing is greater for higher doses.[10]

# Simulations

| Simulation Group | Day 29: Resumed Time & Dose (mg) | Day 30: Resumed Time & Dose (mg) |
|---|---|---|
| 0 (Per Schedule) | Scheduled Time: 1600 | Scheduled Time: 1600 |
| 1 (Delay 12 h) | 12 h to Next Dose: 1600, 2400, or 3200 | Scheduled Time: 1600 |
| 2 (Delay 16 h) | 8 h to Next Dose: 1600, 2400, or 3200 | Scheduled Time: 1600 |
| 3 (Delay 18 h) | 6 h to Next Dose: 1600, 2400, or 3200 | Scheduled Time: 1600 |
| 4 (Delay 20 h) | 4 h to Next Dose: 1600, 2400 or 3200 | Scheduled Time: 1600 |
| 5 (Delay 24 h) | Missed Dose | Scheduled Time: 1600, 2400, or 3200 |
| 6 (Delay 36 h) | Missed Dose | 12 h to Next Dose: 1600, 2400, or 3200 |
| 7 (Delay 40 h) | Missed Dose | 8 h to Next Dose: 1600, 2400, or 3200 |
| 8 (Delay 42 h) | Missed Dose | 6 h to Next Dose: 1600, 2400, or 3200 |
| 9 (Delay 44 h) | Missed Dose | 4 h to Next Dose: 1600, 2400, or 3200 |
| 10 (Delay 48 h) | Missed Dose | Missed Dose |

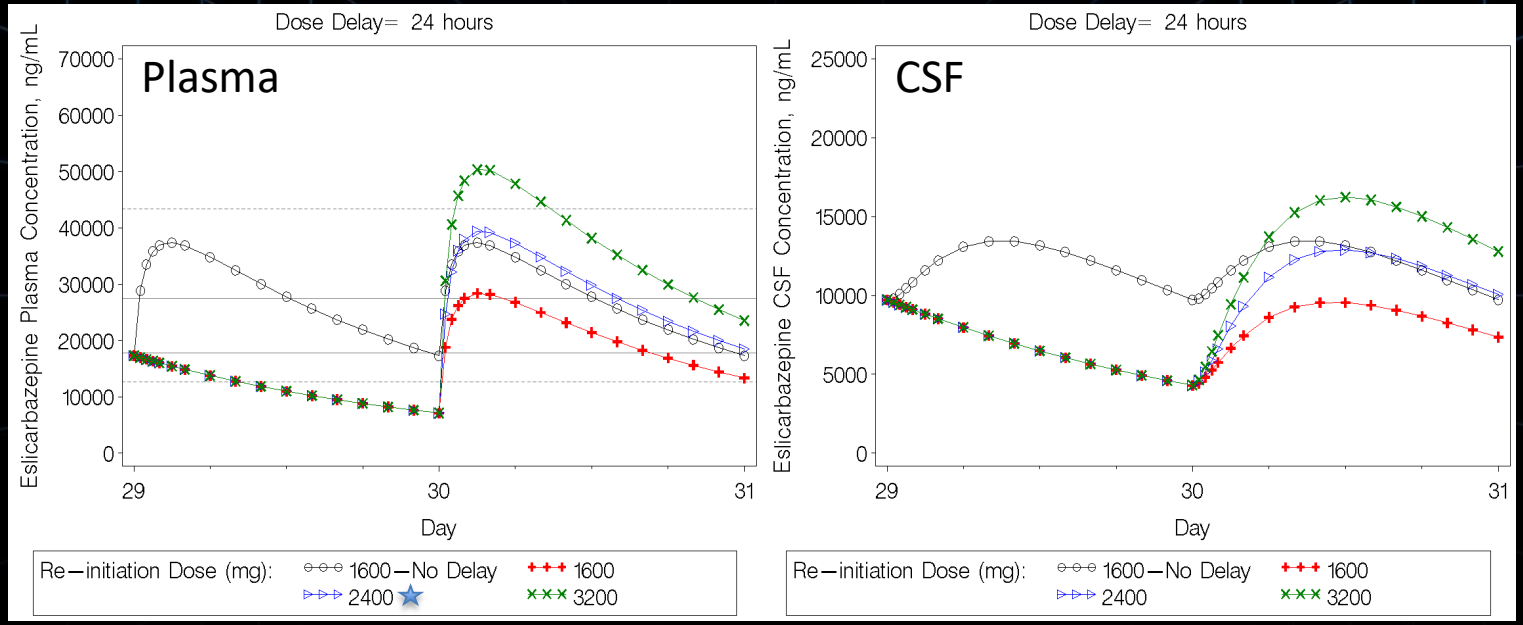
Day 31: All doses at scheduled time with 1600 mg

# Select Simulation Results




Simulations of doses delayed 36-44 hours displayed similar results upon resumption of dosing

# Select Simulation Results




Simulations of doses delayed 48 hours displayed similar results upon resumption of dosing

# Conclusions

- While exploratory, the CSF PK model adequately predicted concentrations.
- Simulations of plasma concentrations suggested that a single missed dose of ESL:
  - remembered more than 4 hours before the next scheduled dose
    - should be taken as soon as remembered, and
    - resume dosing at the original scheduled time
  - remembered within 4 hours of the next scheduled dose time
    - Skip the dose (do not resume until the original scheduled time)
    - at original scheduled time, resume with a single dose 1.5 times higher than the prescribed dose
    - on the following day at the original scheduled time, resume the originally prescribed dosing regimen
- The prescribed dose should NOT be doubled following delayed and missed doses.

# Publication of Presentation

- Sunkaraneni S, Blum D, Ludwig E, Chudasama V, Fiedler-Kelly J, Marvanova M, Bainbridge J, and Phillips L. Population pharmacokinetic evaluation and missed-dose simulations for eslicarbazepine acetate monotherapy in patients with partial-onset seizures. *Clinical Pharmacology in Drug Development.* 2018;7(3): 287–297.

- Thank you to all the co-authors.

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# Q&A

Questions & Answers

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