A 15/92 mg dose of VI-0521 (PHEN/TOPI) would result in a 18%, 51% and 183% increase in Topiramate exposure, respectively. In a typical patient, Topiramate exposure is increased by 18%, 78% and 123% in subjects with varying degrees of renal impairment.

The objectives of the population pharmacokinetic (PK) modeling and simulations were:

1. Conduct modeling and simulation using the phenytoin (PHEN) and modified-release topiramate (TOPI) data from a single dose VI-0521 (fixed-dose combination of PHEN/TOPI) renal impairment study to predict PHEN and TOPI exposure following the recommended titration/maintenance schedule.

2. Make dosing recommendations in subjects with varying degrees of renal impairment.

**METHODS:** Population PK modeling of PHEN and TOPI was performed using Phoenix NLME v1.3, with the extended error model, PROPORTIONAL and LINEAR elimination models. Population PK modeling was performed using Phoenix NLME v1.3.

**RESULTS:** Population PK modeling and simulations allowed the efficacy and safety profiles of the product to be optimized.

**CONCLUSIONS:**

- PHEN and TOPI were adequately fit with 1- and 2-compartment models, respectively.
- The model was used to optimize the titration/maintenance schedule of VI-0521 in patients with normal renal function.
- No dose adjustments are necessary in patients with mild renal impairment.
- In patients with moderate and severe renal impairment, the dose should not exceed VI-0521 7.5 mg per day.
- The maximum VI-0521 maintenance dose is reduced by 50% as compared to patients with normal renal function.
- Ultimately, population PK modeling and simulations allowed the efficacy and safety profiles of the product to be optimized.

**REFERENCES**