# MODELING AND SIMULATIONS OF A FIXED-DOSE COMBINATION PRODUCT OF IMMEDIATE-RELEASE PHENTERMINE AND MODIFIED-RELEASE TOPIRAMATE (VI-0521) TO SUPPORT DOSING REGIMEN IN PATIENTS WITH HEPATIC IMPAIRMENT

Mohamad-Samer Mouksassi[1], MyMy Trinh[1], Colin Chang[1], JF Marier[1], Craig Peterson[2], and Shiyin Yee[2]
[1]Pharsight - A Certara™ Company (Montreal, Canada), [2]Vivus Inc. (Mountain View, CA, USA)

## ABSTRACT

**BACKGROUND:** VI-0521 is a fixed-dose combination product of immediate-release phentermine (PHEN) and modified-release topiramate (TOPI) currently approved for the treatment of obesity. Population PK modeling and simulations were performed to support dosing of VI-0521 in subjects with mild and moderate hepatic impairment.

**METHODS:** Population PK modeling of PHEN and TOPI was performed and the effect of hepatic impairment was evaluated. Simulations were performed to optimize VI-0521 dosing regimen in subjects with moderate hepatic impairment according to the therapeutic range of the products. Modeling and Simulations were performed using Phoenix NLME V1.3.

**RESULTS:** PHEN and TOPI were adequately fitted with 1- and 2-compartment models, respectively. Absorption of PHEN and TOPI were described using lag times and first-order rate constants. Subjects with mild and moderate hepatic impairment are expected to display steady-state PHEN exposure 25% and 41% higher than subjects with normal hepatic function, respectively, whereas topiramate exposure is not increased in these hepatic impairment groups. No dose adjustments are necessary in patients with mild hepatic impairment. The recommended starting dose of VI-0521 (PHEN/TOPI) in subjects with mild hepatic impairment is 3.75/23 mg q24 for 14 days, followed by 7.5/46 mg q24. Titration to 11.25/69 mg q24 for 14 days, followed by a maintenance dose of 15/92 mg q24 should be considered if weight loss goals have not been achieved after 12 weeks. For subjects with moderate hepatic impairment, the same starting dose of VI-0521 is recommended, followed by a maximum maintenance dose of 7.5/46 mg q24.

**CONCLUSION:** Population PK modeling was performed to assess the effect of hepatic impairment on PHEN and TOPI exposure. Simulations were used to optimize dosing and titration schemes of VI-0521 in subjects with liver impairment and ultimately optimize the efficacy and safety profiles of the product.

## OBJECTIVES

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

1. Conduct modeling and simulation using the phentermine (PHEN) and modified-release topiramate (TOPI) data from a single dose of VI-0521 (a fixed-dose combination of PHEN/TOPI) hepatic impairment study to predict PHEN and TOPI exposure following the recommended titration/maintenance schedule
2. Make a dosing recommendation in subjects with varying degrees of hepatic impairment.

## METHODOLOGY

### STUDY DESIGN AND POPULATION

- A Phase I, open label, single dose study in 16 subjects with mild to moderate hepatic impairment (Child-Pugh Classification System) and in 8 subjects with normal hepatic function.
- Subjects were male or female, between 39 and 62 years of age (inclusive), with body weights between 58.6 to 112 kg, and body mass index (BMI) between 22 kg/m$^2$ and 38.0 kg/m$^2$.
- One VI-0521 capsule containing 15 mg phentermine (as base) and 92 mg topiramate was administered under fasted conditions
- A total of 18 blood samples were collected at predose and up to 192 h post-dose for the determination of PHEN and TOPI concentrations in plasma.
- Plasma samples were analyzed for PHEN and TOPI using a validated liquid chromatography with tandem mass spectrometric (LC/MS/MS) detection method.
- Population PK modeling was performed using Phoenix™ NLME v1.3, with the extended least-squares first-order conditional estimation (FOCE-ELS) and the INTERACTION option.
- All subjects were included in the population PK analysis.

## RESULTS: POPULATION PK MODELS

### FINAL MODEL OF PHENTERMINE AND TOPIRAMATE

Candidate structural models were fit to the 383 and 409 plasma concentrations of PHEN and TOPI, respectively.

**Figure 1. Population PK Model Development**

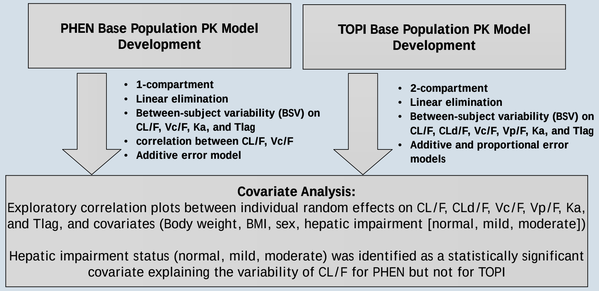



**Table 1. Population PK Parameters of Phentermine - Final Model**

| Population PK Parameters | Typical Values | BSV% (Shrinkage %) |
|---|---|---|
| **Ka (1/h)** | 0.899 | 83.5 (12.0) |
| **Tlag (h)** | 0.05 | 198.0 (42.6) |
| **CL/F (L/h)** | | |
| Normal Hepatic Function | 7.12 | |
| Mild Hepatic Impairment | 5.29 | 26.5 (4.1) |
| Moderate Hepatic Impairment | 5.01 | |
| **V/F (L)** | 270 | 17.6 (2.8) |
| **Error Model** | | |
| Additive error (ng/mL) | 3.24 | NA |

BSV= Between subject variability, CL/F= Apparent systemic clearance, Ka= first-order rate constant, V/F= Apparent volume of distribution, Tlag=Lag time, NA= Not applicable.
Note: Correlation between between CL/F and V/F was 0.521.

**Table 2. Population PK Parameters of Topiramate - Final Model**

| Population PK Parameters | Typical Values | BSV% (Shrinkage %) |
|---|---|---|
| **Ka (1/h)** | 0.371 | 14.2 (19.6) |
| **Tlag (h)** | 0.598 | 25.3 (7.9) |
| **CL/F (L/h)** | 1.036 | 27.5 (0.60) |
| **Cld/F (L/h)** | 0.316 | 34.6 (18.6) |
| **Vc/F (L)** | 59.9 | 32.0 (0.5) |
| **Vp/F (L)** | 36.5 | 1.06 (99.3) |
| **Error Model** | | |
| Additive error (ng/mL) | 7.13 | NA |
| Proportional error (%) | 0.0508 | NA |

BSV= Between subject variability, CL/F= Apparent central systemic clearance, Ka= first-order rate constant, Vc/F= Apparent central volume of distribution. CLd/F= Apparent peripheral systemic clearance, Vp/F= Apparent peripheral volume of distribution, NA= Not applicable.

- The individual PK parameters derived from the final population PK models were used to perform simulations to predict the steady-state exposure to PHEN and TOPI in subjects with normal and impaired hepatic function (mild and moderate hepatic impairment). Refer to Tables 3 and 4.

## RESULTS: SIMULATIONS

### SIMULATIONS - FINAL MODEL OF PHENTERMINE

**Table 3. Mean (CV%) Plasma PK Parameters of Phentermine for Varying Degrees of Hepatic Function - Once Daily Dosing of Phentermine 15 mg**

| Hepatic Function | Child-Pugh Scores (points)[a] | Mean (CV%) CL/F (L/h) | Mean (CV%) t½ (h) | Mean (CV%) AUCss (ng.h/mL) for 15 mg Phentermine | AUCss Ratio Relative to Normal Hepatic Function |
|---|---|---|---|---|---|
| Normal Hepatic Function | NA | 7.08 (24.7%) | 26.7 (22.4%) | 2232 (24.5%) | NA |
| Mild Hepatic Impairment | 5 to 6 | 5.77 (26.8%) | 36.4 (19.2%) | 2788 (30.3%) | 1.25 |
| Moderate Hepatic Impairment | 7 to 9 | 5.04 (24.2%) | 38.4 (25.6%) | 3157 (29.6%) | 1.41 |

[a]Points Scored for Increasing Abnormality (Child-Pugh Method, J Gastroenterol Hepatol 1996; 11:33).
NA= Not applicable

- A 15/92 mg dose of VI-0521 (PHEN/TOPI) would result in a 25% and a 41% higher steady state exposure (AUCss) to phentermine for a typical patient with mild or moderate hepatic impairment, respectively, as compared to that observed in patients with normal hepatic function.

### SIMULATIONS - FINAL MODEL OF TOPIRAMATE

**Table 4. Mean (CV%) Plasma PK Parameters of Topiramate for Varying Degrees of Hepatic Function - Once Daily Dosing of Topiramate at Various Doses**

| Hepatic Function | Child-Pugh Scores (points)[a] | Mean (CV%) CL/F (L/h) | Mean (CV%) t½ (h) | PK Parameters | Mean (CV%) 23 mg (Low) | 46 mg (Mid) | 69 mg (¾ Top) | 92 mg (Top) |
|---|---|---|---|---|---|---|---|---|
| Normal Hepatic Function | NA | 1.06 (17.4%) | 119 (16.0%) | $AUC_{ss}$ (ng.h/mL) | 18690 (15.9) | 43708 (15.4) | 62807 (15.7) | 88492 (15.8) |
| | | | | $C_{max}$ (ng/mL) | 884 (17.3) | 2041 (16.4) | 2942 (16.7) | 4128 (16.6) |
| | | | | $C_{min}$ (ng/mL) | 623 (14.5) | 1533 (14.5) | 2174 (14.6) | 3114 (14.9) |
| Mild Hepatic Impairment | 5 to 6 | 1.04 (40.8%) | 129 (25.6%) | $AUC_{ss}$ (ng.h/mL) | 23020 (30.3) | 47544 (31.0) | 72354 (31.4) | 98530 (32.0) |
| | | | | $C_{max}$ (ng/mL) | 1065 (30.3) | 2194 (30.9) | 3336 (31.2) | 4536 (31.7) |
| | | | | $C_{min}$ (ng/mL) | 813 (30.3) | 1692 (31.2) | 2584 (31.7) | 3537 (32.4) |
| Moderate Hepatic Impairment | 7 to 9 | 1.13 (30.2%) | 118 (30.1%) | $AUC_{ss}$ (ng.h/mL) | 20564 (27.8) | 43865 (30.2) | N/A | N/A |
| | | | | $C_{max}$ (ng/mL) | 956 (27.5) | 2029 (29.6) | N/A | N/A |
| | | | | $C_{min}$ (ng/mL) | 722 (28.6) | 1564 (31.6) | N/A | N/A |

N/A= Not applicable
[a]Points Scored for Increasing Abnormality (Child-Pugh Method, J Gastroenterol Hepatol 1996; 11:33).

- A 7.5/46 mg dose of VI-0521 (PHEN/TOPI) would not result in increases in steady state exposure (AUCss) to topiramate for a typical patient with mild or moderate hepatic impairment, as compared to that observed in patients with normal hepatic function.

### FINAL DOSING RECOMMENDATIONS

The individual parameters from the population PK model were used to perform simulations using the following dosing regimens:

a) VI-0521 (PHEN/TOPI) in subjects with normal hepatic function and mild hepatic impairment is 3.75/23 mg q24 for 14 days, followed by 7.5/46 mg q24. Titration to 11.25/69 mg q24 for 14 days, followed by a maintenance dose of 15/92 mg q24 may be considered if weight loss goals have not been achieved after 12 weeks.

b) For subjects with moderate hepatic impairment, the same starting dose of VI-0521 is recommended for 14 days, followed by a maximum maintenance dose of 7.5/46 mg q24.

## RESULTS: DOSING RECOMMENDATIONS

**Figure 2. Predicted Plasma Phentermine Concentration-Time Profile in Patients Following the Recommended Dose - By Hepatic Function**

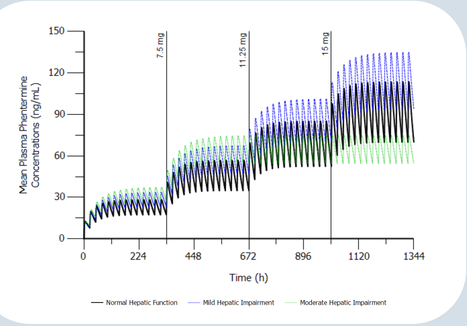
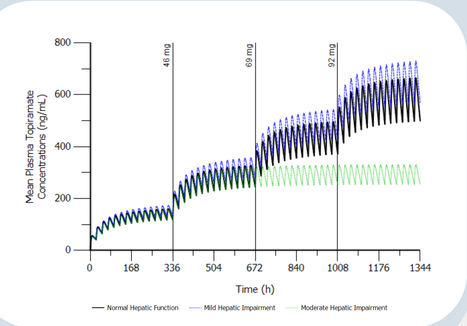



**Figure 3. Predicted Plasma Topiramate Concentration-Time Profile in Patients Following the Recommended Dose - By Hepatic Function**




## CONCLUSIONS

- PHEN and TOPI were adequately fitted with 1- and 2-compartment models, respectively.
- Simulations were used to optimize the titration/maintenance schedule of VI-0521 in patients with liver impairment.
- No dose adjustments are necessary in patients with mild hepatic impairment.
- For moderate hepatic impairment, dosing should not exceed VI-0521 7.5 mg/46 mg q24. The maximum VI-0521 maintenance dose is reduced by 50% as compared to patients with normal hepatic function and mild hepatic impairment.
- Ultimately, population PK modeling and simulations allowed the efficacy and safety profiles of the product to be optimized.

## REFERENCES

- Child-Pugh Method, J Gastroenterol Hepatol 1996; 11:33