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

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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, moderate or severe renal impairment.

METHODS: Population PK modeling of PHEN and TOPI was performed and the effect of renal impairment was evaluated. Simulations were performed to optimize VI-0521 dosing regimen in subjects with renal 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. Based on simulations, subjects with mild, moderate and severe renal impairment displayed steady-state PHEN exposure 1.2-, 1.5- and 2.8-fold higher than healthy subjects, respectively. Similar increases in steady-state TOPI exposure were observed relative to healthy subjects. No dose adjustments are necessary in patients with mild renal impairment. The recommended starting dose of VI-0521 (PHEN/TOPI) in subjects with mild renal 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 and the treatment is well tolerated. For subjects with moderate or severe renal impairment, the same starting dose of VI-0521 is recommended, followed by a maximum dose of 7.5/46 mg q24.

CONCLUSION: Population PK modeling was performed to assess the effect of renal impairment on PHEN and TOPI exposure. Simulations were used to optimize dosing and titration schemes of VI-0521 in subjects with renal 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) 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.

METHODOLOGY

STUDY DESIGN AND POPULATION

- A Phase I, open label, single dose study in 25 subjects with mild to severe renal impairment and in 8 subjects with normal renal function.
- Subjects were male or female, between 50 and 78 years of age (inclusive), with body weights between 52.5 to 93.7 kg, and body mass index (BMI) between 19.1 kg/m^2 and 34.4 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 21 blood samples were collected at pre-dose 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 iterative two-stage (IT2S-EM), along with the INTERACTION option.
- All subjects were included in the population PK analysis, with the exception of one subject who discontinued from the study on Day 2 (no PHEN or TOPI samples were drawn from 24 to 192 hours post-dose).

RESULTS: POPULATION PK MODELS

FINAL MODEL OF PHENTERMINE AND TOPIRAMATE

Candidate structural models were fit to 620 and 640 plasma concentrations of PHEN and TOPI, respectively.

Figure 1. Population PK Model Development

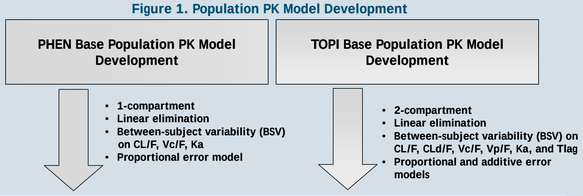


Table 1. Population PK Parameters of Phentermine - Final Model

Population PK Parameters	Typical Values	BSV% (Shrinkage %)
Ka (1/h)	0.627	74.8 (5.39)
CL/F (L/h)		
Normal Renal Function	6.20	
Mild Renal Impairment	5.12	30.3 (1.22)
Moderate Renal Impairment	4.19	
Severe Renal Impairment	2.36	
V/F (L)	222	20.5 (3.27)
Error Model		
Proportional error (%)	15.1	NA

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

Table 2. Population PK Parameters of Topiramate - Final Model

Population PK Parameters	Typical Values	BSV% (Shrinkage %)
Ka (1/h)	0.360	20.1 (12.4)
Tlag (h)	0.582	28.8 (12.4)
CL/F (L/h)		
Normal Renal Function	0.904	
Mild Renal Impairment	0.754	14.6 (6.3)
Moderate Renal Impairment	0.506	
Severe Renal Impairment	0.405	
Cld/F (L/h)	0.206	2.4 (96.9)
Vc/F (L)	45.4	21.6 (-0.61)
Vp/F (L)	7.74	147.7 (29.1)
Error Model		
Additive error (ng/mL)	32.0	NA
Proportional error (%)	4.30	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 renal function (mild, moderate and severe renal 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 Renal Function - Once Daily Dosing of Phentermine 15 mg

Renal Function	(CLCr)[a] (mL/min)	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 Renal Function
Normal Renal Function	≥80	6.47 (24.6)	23.4 (17.8)	2449 (26.0)	NA
Mild Renal Impairment	≥50 – <80	5.30 (14.1)	28.4 (24.8)	2889 (16.7)	1.18
Moderate Renal Impairment	≥30 – <50	4.24 (21.3)	38.8 (22.1)	3700 (24.2)	1.51
Severe Renal Impairment	<30	2.72 (45.3)	77.2 (48.9)	6929 (54.6)	2.83

[a]Creatinine clearance estimated by Cockcroft-Gault formula.
NA= Not applicable

- A 15/92 mg dose of VI-0521 (PHEN/TOPI) would result in a 18% , 51% and 183% higher steady state exposure (AUCss) to phentermine for a typical patient with mild, moderate or severe renal impairment, respectively, as compared to that observed in patients with normal renal function.

SIMULATIONS - FINAL MODEL OF TOPIRAMATE

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

Renal Function	(CLCr)[a] (mL/min)	CL/F (L/h)	t½ (h)	PK Parameter	Mean (CV%) 23 mg (Low)	46 mg (Mid)	69 mg (¾ Top)	92 mg (Top)
Normal Renal Function	≥80	0.909 (8.5)	69.1 (22.6)	AUC_{ss} (ng.h/mL)	22909 (9.9)	50792 (8.4)	73697 (8.8)	101835 (8.3)
				C_{max} (ng/mL)	1064 (10.3)	2356 (8.6)	3424 (9.0)	4723 (8.5)
				C_{min} (ng/mL)	771 (9.8)	1786 (8.5)	2561 (8.7)	3583 (8.4)
Mild Renal Impairment	≥50 – <80	0.771 (12.8)	73.7 (20.5)	AUC_{ss} (ng.h/mL)	29503 (13.6)	59726 (13.4)	89983 (13.3)	121037 (13.1)
				C_{max} (ng/mL)	1364 (12.9)	2760 (12.7)	4157 (12.6)	5589 (12.4)
				C_{min} (ng/mL)	1044 (15.6)	2121 (15.3)	3199 (15.2)	4315 (15.0)
Moderate Renal Impairment	≥30 – <50	0.519 (20.1)	123.7 (81.5)	AUC_{ss} (ng.h/mL)	44933 (18.5)	90505 (18.1)	136179 (17.9)[b]	182446 (17.8)[b]
				C_{max} (ng/mL)	2011 (17.8)	4049 (17.5)	6091 (17.3)[b]	8158 (17.2)[b]
				C_{min} (ng/mL)	1675 (19.9)	3377 (19.5)	5084 (19.3)[b]	6816 (19.2)[b]
Severe Renal Impairment	<30	0.411 (15.2)	106.9 (75.8)	AUC_{ss} (ng.h/mL)	56381 (18.3)	113462 (17.6)	170804 (17.5)[b]	228638 (17.1)[b]
				C_{max} (ng/mL)	2488 (18.7)	5006 (18.1)	7536 (17.9)[b]	10085 (17.5)[b]
				C_{min} (ng/mL)	2152 (17.9)	4335 (17.2)	6530 (17.1)[b]	8745 (16.7)[b]

[a]Creatinine clearance estimated by Cockcroft-Gault formula
[b] Dosing regimens are not recommended. Shown for information purposes. NA= Not applicable

- Topiramate exposure is increased by 18%, 78% and 123% in a typical patient with mild, moderate or severe renal impairment, respectively, compared to that observed in patients with normal renal function

Final Dosing Recommendations

a) VI-0521 (PHEN/TOPI) in subjects with normal renal function and mild renal 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 if weight loss goals have not been achieved after 12 weeks.

b) For subjects with moderate and severe renal impairment, the same starting dose of VI-0521 is recommended, followed by a maximum 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 Renal Function

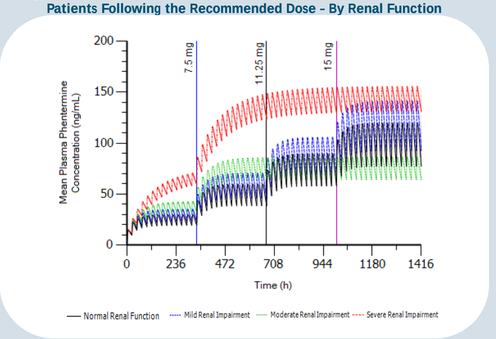
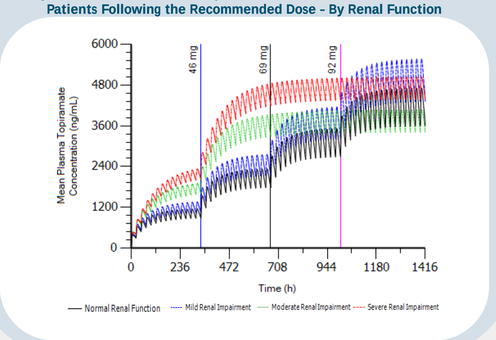


Figure 3. Predicted Plasma Topiramate Concentration-Time Profile in Patients Following the Recommended Dose – By Renal Function



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 renal impairment .
- 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/46 mg q24. The maximum VI-0521 maintenance dose is reduced by 50% as compared to patients with normal renal function and mild renal impairment.
- Ultimately, population PK modeling and simulations allowed the efficacy and safety profiles of the product to be optimized.

REFERENCES

Cockcroft DW, Gault MH. Prediction of Creatinine Clearance from Serum Creatinine. Nephron. 1976;16:31-41.