MODELING AND SIMULATIONS TO DETERMINE THE EFFECT OF A FIXED-DOSE COMBINATION PRODUCT OF IMMEDIATE-RELEASE PHENTERMINE AND MODIFIED-RELEASE TOPIRAMATE (VI-0521) ON HEART RATE IN OBESE PATIENTS

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INTRODUCTION

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. The Phase 3 program investigated the following three dose levels of VI-0521 (PHEN/TOPI): Low dose (3.75/23 mg), Mid or recommended dose (7.5/46 mg), and Top dose (15/92 mg).

The incidence of TEAEs of cardiac arrhythmia was reported to be higher in the VI-0521 Top-dose group (4.7%) and mid-dose group (4.2%) as compared to those observed for the placebo group (1.8%). Palpitations, increased heart rate, and tachycardia represented 36 of the 41 cardiac arrhythmia TEAEs observed in the 1-year cohort.

OBJECTIVES

To develop a pharmacokinetic-pharmacodynamic (PK/PD) model to assess the relationship between PHEN concentrations and heart rate (HR) and ultimately predict the effect of VI-0521 on 24-hour HR profile in obese patients.

METHODOLOGY

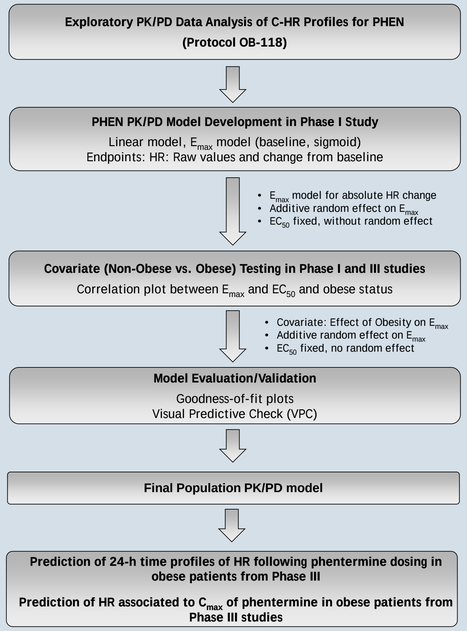
PK/PD modeling was performed in a stepwise manner (Fig. 1), based on rich PK and HR data collected in a thorough QT Phase I study (OB-118; n=55) in non-obese subjects and sparse data collected in obese patients enrolled in 3 Phase III studies (OB-301, OB-302, and OB-303; n=1845) (Table 1 and 2). The effect of disease status (non-obese vs. obese) on PD parameters was evaluated after combining Phase I and III studies. Simulations were performed to determine the effect of VI-0521 on 24-hour change from baseline HR profiles (ΔHR) and maximum effect (ΔHRmax) in obese patients. Modeling and Simulations were performed using Phoenix® NLME™ V1.3.

Table 1. Baseline Characteristics of Population Studied

Study (Number of Subjects)	Mean [Minimum-Maximum]		
	Baseline Heart Rate (beat/min)	Body Weight (kg)	Age (years)
OB-118 (55)	65.0 [46-92]	72.8 [52.6 - 92]	32.5 [19-48]
OB-301 (290)	71.1 [47-100]	102 [67.2-166.6]	45.8 [18.4-70.0]
OB-302 (504)	72.7 [47-108]	116.6 [73.6-217]	42.8 [18.1-71.0]
OB-303 (1051)	71.9 [44-116]	103 [57.6-162.8]	51.2 [22.2-70.9]
Overall (1900)	71.8 [44-116]	105.6 [52.6-217]	47.6 [18.1-71.0]

METHODOLOGY

Figure 1. Population PKPD Model Development



EC_{50}= concentration producing 50% of the maximal difference between the baseline and the maximum effect (E_{max}); E_{max}= maximum effect; HR= heart rate; PD= pharmacodynamics; PHEN= phentermine; PK= pharmacokinetics; VPC= visual predictive check

RESULTS

- A maximum effect model (Emax) and effective concentrations associated to 50% of the Emax (EC50) resulted in adequate goodness-of-fit .
- The proposed PK/PD model adequately predicted the HR data collected in Phase I and III studies with predicted 5, 50 and 95th percentiles values close to the observed percentiles (Fig. 2).
- The proposed PK/PD model adequately predicted resulted in adequate goodness-of-fit. Weighted residuals were homogeneously distributed (Fig. 3).
- A disease effect was observed on Emax. This suggest that the maximum effect was different in obese and non-obese, with obese patients displaying less of an effect.

RESULTS

Figure 2. VPC: Phentermine Concentrations versus Heart Rate Change from Baseline in Phases I and III Studies

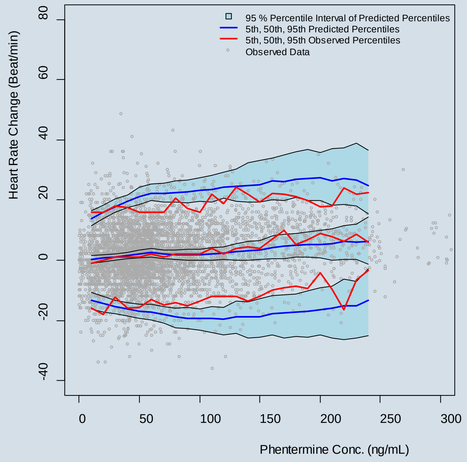
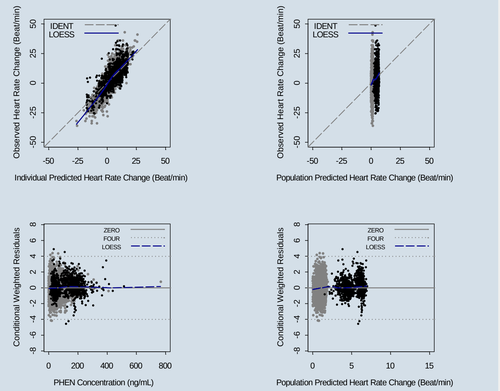


Figure 3. Goodness of Fit: Population PK/PD Model for Heart Rate Change from Baseline in Non-Obese and Obese Subjects



IDENT= identity line; LOESS= locally weighted scatterplot smoothing; PHEN= phentermine

Black symbols represent the data from study OB-118 (non-obese subjects); gray symbols represent the data from the 3 other Phase III studies (obese subjects)

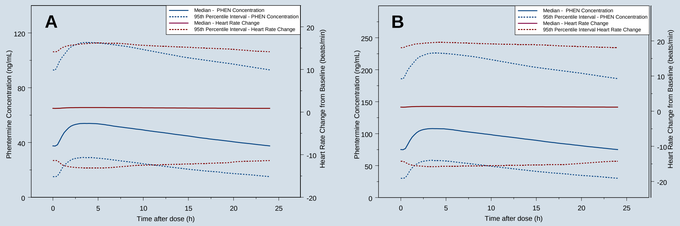
RESULTS

Table 2. Population PD Parameters in Non-Obese and Obese Subjects

PK/PD Parameter	Typical Value (RSE)	BSV (RSE)
EC_{50} (ng/mL)	32.5 (0 FIX)	0 FIX
E_{max} Non-Obese (beats/min)	7.45 (24.0 %)	11.6 beats/min (2.05 %)
E_{max} Obese (beats/min)	2.02 (126.2 %)	
Additive error (beats/min)	6.92 (0.617 %)	-

- Typical Emax values in non-obese and obese subjects were 7.45 and 2.02 beat/min, respectively.

Figure 4. Phentermine Concentrations vs. Heart Rate (%Δ) over 24-hours in Phase III Studies - A) VI-0521 Mid Dose Level; B) VI-0521 Top Dose Level



- Based on simulations performed with the PK/PD model, median ΔHRmax (95 % prediction intervals) associated to PHEN doses of 3.75, 7. 5 and 15 mg were 0.7 beats/min (-8.1 to +12.0), 1.1 beats/min (-12.4 to +15.4; Fig. 4A), and 1.4 beats/min (-14.3 to +19.6; Fig. 4B), respectively.

CONCLUSION

PK/PD modeling and simulations were performed to determine the maximum effect of PHEN on HR profiles in obese patients. Results derived with the PK/PD model are consistent with those published by Hendrick et al. (2011), suggesting no significant effect on HR following long term administration of 15 to 37.5 mg/day of PHEN in obese subjects (i.e., +1.2 beats/min at Week 52).

In addition, weight loss secondary to phentermine treatments was reported to result in a favorable shifts in categorical blood pressure and retardation of progression to hypertension in obese patients (Hendrick et al., 2011).

PK/PD modeling of topiramate was not performed due to lack of effect on HR.

REFERENCES

Hendricks EJ, Greenway FL, Westman EC, Gupta AK. Blood pressure and heart rate effects, weight loss and maintenance during long-term phentermine pharmacotherapy for obesity. Obesity. 2011 Dec;19(12):2351-60.

Vivus, Inc (2010). VI-0521 (QNEXA®) Advisory Committee Briefing Document, NDA 022580.