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

Thomas Peyret1, Nathalie H. Gosselin1, Mohamad-Samer Mouksassi1, JF Marier1, Shiyin Yee2, and Wesley W. Day2
1Pharsight - A Certara™ Company (Montreal, Canada), 2VIVUS, Inc. (Mountain View, CA)

INTRODUCTION

VI-0521 is a fixed-dose combination product of immediate-release phentermine (PHEN) and modified-release topiramate (TOP) currently approved for the treatment of obesity. The Phase 3 program investigated the following three dose levels of VI-0521 (PHEN/TOP): 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 (4.2%) 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-301, 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 baseline HR profiles and maximum effect (HRmax) in obese patients. Modeling and Simulations were performed using Phoenix® NLME™ V1.3.

RESULTS

• A maximum effect model (Emax) and effective concentrations associated to 50% of the Emax (ECS0) 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 close to the observed percentiles (Fig. 2).
  - The proposed PK/PD model adequately predicted 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 in obese was different in non-obese, with obese patients displaying less of an effect.

- 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 +19.4; 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 from 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
