**SUPPLEMENTARY INFORMATION for** "Physiologically-Based Pharmacokinetic Model for Predicting Drug-Drug Interactions Perpetrated by Posaconazole in Healthy Subjects with Normal Weight and Obesity: Concomitant Use and Washout"

**Authors**: Christopher D. Bruno[1,2], Ahmed Elmokadem[3], David J. Greenblatt[2], Christina R. Chow[1]

**Affiliations**: 1) Emerald Lake Safety, LLC, Newport Beach, CA, USA. 2) Program in Pharmacology and Drug Development, Tufts University School of Medicine; and the Clinical and Translational Science Institute, Tufts Medical Center, Boston, MA, USA. 3) Metrum Research Group, Tariffville, Connecticut, USA

**Corresponding Author**: Christina R. Chow, PhD, 23 Corporate Plaza Drive, Suite 150, Newport Beach, CA 92660. Email: christina@elsafety.com.

**Virtual Population**:
Below is a summary of the demographics of the virtual population.

**Supplementary Table 1: Virtual Population Demographics**

| | COHORT | |
|---|---|---|
| | **Normal Weight (N = 500)** | **Obesity (N = 500)** |
| Age (years) | 34.4 (9.1) [19 - 50] | 34.1 (9) [19 - 50] |
| Weight (kg) | 64.8 (8.3) [48.3 - 87] | 106.4 (11.9) [80.7 - 137.8] |
| Height (cm) | 168.9 (8.8) [150.1 - 189] | 167.9 (9.3) [150.5 - 189.1] |
| BMI ($kg/m^2$) | 22.6 (1.5) [18.6 - 24.9] | 37.7 (2.4) [35 - 47.9] |
| Sex* | Female: 250 (50%) Male: 250 (50%) | Female: 250 (50%) Male: 250 (50%) |

Data presented as mean (standard deviation) [range].
* Data presented as N (%)

**DDI Validation:**

BOW-001[1] and BOW-002[2] studies were simulated according to study protocols using the virtual population described in the manuscript. Below are the tables for $AUC_{inf}$ and $C_{max}$, as well as the ratios of $AUC_{inf}$ and $C_{max}$ relative to study day 1. Observed and Predicted data are presented as geometric means. All calculated GMFEs are within the 2-fold error criteria for acceptability:

**Supplementary Table 2: BOW-001 (ranolazine) DDI Validation**

| | | $AUC_{inf}$ (ng*h/mL) | | | AUC Ratio | | |
|---|---|---|---|---|---|---|---|
| **Cohort** | **Study Day** | **Observed** | **Predicted** | **GMFE** | **Observed** | **Predicted** | **GMFE** |
| Normal Weight | 1 | 6,262 | 5,151 | 1.22 | - | - | - |
| | 15 | 21,771 | 14,065 | 1.55 | 3.48 | 2.73 | 1.27 |
| | 18 | 15,804 | 12,556 | 1.26 | 2.52 | 2.44 | 1.03 |
| | 22 | 11,375 | 8,935 | 1.27 | 1.8 | 1.73 | 1.04 |
| | 25 | 8,368 | 7,177 | 1.17 | 1.33 | 1.39 | 1.05 |
| | 29 | 7,284 | 5,947 | 1.22 | 1.17 | 1.15 | 1.01 |
| Obesity | 1 | 3,857 | 4,867 | 1.26 | - | - | - |
| | 15 | 16,924 | 13,359 | 1.27 | 2.14 | 2.79 | 1.3 |
| | 18 | 13,908 | 12,494 | 1.11 | 1.72 | 2.61 | 1.51 |
| | 22 | 12,597 | 10,122 | 1.24 | 1.52 | 2.1 | 1.38 |
| | 25 | 10,979 | 8,451 | 1.3 | 1.34 | 1.75 | 1.31 |
| | 29 | 8,403 | 6,775 | 1.24 | 1.01 | 1.41 | 1.39 |

| | | $C_{max}$ (ng/mL) | | | $C_{max}$ Ratio | | |
|---|---|---|---|---|---|---|---|
| **Cohort** | **Day** | **Observed** | **Predicted** | **GMFE** | **Observed** | **Predicted** | **GMFE** |
| Normal Weight | 1 | 605.9 | 323.3 | 1.87 | - | - | - |
| | 15 | 1,209.7 | 842.5 | 1.44 | 2 | 2.61 | 1.31 |
| | 18 | 1,117.9 | 777.9 | 1.44 | 1.84 | 2.41 | 1.31 |
| | 22 | 820.1 | 576.0 | 1.42 | 1.35 | 1.78 | 1.32 |
| | 25 | 828.6 | 468.8 | 1.77 | 1.35 | 1.45 | 1.07 |
| | 29 | 669.8 | 391.9 | 1.71 | 1.11 | 1.21 | 1.09 |
| Obesity | 1 | 504.5 | 267.4 | 1.89 | - | - | - |
| | 15 | 962.4 | 696.3 | 1.38 | 1.91 | 2.65 | 1.39 |
| | 18 | 927.7 | 665.7 | 1.39 | 1.79 | 2.53 | 1.41 |
| | 22 | 970.3 | 560.6 | 1.73 | 1.92 | 2.12 | 1.1 |
| | 25 | 877.2 | 478.6 | 1.83 | 1.72 | 1.81 | 1.05 |
| | 29 | 668.8 | 391.6 | 1.71 | 1.33 | 1.48 | 1.12 |

**Supplementary Table 3: BOW-002 (lurasidone) DDI Validation**

| | | $AUC_{inf}$ (ng*h/mL) | | | AUC Ratio | | |
|---|---|---|---|---|---|---|---|
| **Cohort** | **Study Day** | **Observed** | **Predicted** | **GMFE** | **Observed** | **Predicted** | **GMFE** |
| Normal Weight | 1 | 46 | 41.06 | 1.12 | - | - | - |
| | 14 | 331.71 | 361.21 | 1.09 | 7.28 | 8.31 | 1.14 |
| | 20 | 257.99 | 239.27 | 1.08 | 5.65 | 5.52 | 1.02 |
| | 23 | 233.79 | 183.5 | 1.27 | 5.13 | 4.24 | 1.21 |
| | 26 | 198.88 | 130.46 | 1.52 | 4.38 | 3.02 | 1.45 |
| | 30 | 153.21 | 80.8 | 1.9 | 3.37 | 1.88 | 1.8 |
| Obesity | 1 | 49.06 | 29.84 | 1.64 | - | - | - |
| | 14 | 205.07 | 340.75 | 1.66 | 4.81 | 8.96 | 1.86 |
| | 20 | 217.77 | 211.89 | 1.03 | 5.05 | 5.71 | 1.13 |
| | 23 | 200.04 | 208.24 | 1.04 | 4.69 | 5.61 | 1.19 |
| | 26 | 232.11 | 225.11 | 1.03 | 5.44 | 6 | 1.1 |
| | 30 | 241.51 | 174.54 | 1.38 | 5.67 | 4.67 | 1.21 |

| | | $C_{max}$ (ng/mL) | | | $C_{max}$ Ratio | | |
|---|---|---|---|---|---|---|---|
| **Cohort** | **Day** | **Observed** | **Predicted** | **GMFE** | **Observed** | **Predicted** | **GMFE** |
| Normal Weight | 1 | 16.56 | 13.19 | 1.26 | - | - | - |
| | 14 | 65.18 | 40.44 | 1.61 | 4 | 3.07 | 1.3 |
| | 20 | 48.89 | 33.05 | 1.48 | 2.99 | 2.51 | 1.19 |
| | 23 | 38.6 | 26.63 | 1.45 | 2.37 | 2.02 | 1.17 |
| | 26 | 27.86 | 21.32 | 1.31 | 1.72 | 1.62 | 1.06 |
| | 30 | 25 | 17.07 | 1.46 | 1.54 | 1.29 | 1.19 |
| Obesity | 1 | 17.45 | 12.9 | 1.35 | - | - | - |
| | 14 | 44.04 | 39.79 | 1.11 | 2.91 | 3.08 | 1.06 |
| | 20 | 37.2 | 33.33 | 1.12 | 2.43 | 2.58 | 1.06 |
| | 23 | 28.68 | 29.24 | 1.02 | 1.89 | 2.27 | 1.2 |
| | 26 | 27.73 | 25.23 | 1.1 | 1.83 | 1.96 | 1.07 |
| | 30 | 22.29 | 20.72 | 1.08 | 1.47 | 1.61 | 1.09 |

**Population PK Modeling:**

A population pharmacokinetic model described in the Noxafil Assessment Report by the EMA[3] (Procedure No. EMEA/H/C/000610/II/0062) Section 2.3.2.8 was recreated using the mrgsolve platform. Briefly, the base structural model consists of a 2-compartment PK model with sequential zero- and first-order absorption and linear elimination parameterized by Ka, CL, Vc, Q, Vd, D1 and F1. Body weight (centered on 70 kg) was used for allometric scaling of CL, Q, Vc, and Vd using estimated exponents reported in the model summary. The exponent for weight effect on CL and Q was estimated to be 0.531, whereas the exponent for weight effect on Vc and Vp was 1.41. Single-dose simulations for individuals weighing 70 kg, 100kg, 120 kg, 140 kg, 160 kg, and 180 kg receiving a 300 mg dose were executed, and subsequent non-compartmental analysis (NCA) was done using PK timepoints at 0, 0.5, 1, 2, 4, 6, 8, 10, 12, 18, 24, 48, 72, 96, and 120 h. Aside from changes in body weight, all patients were assumed to represent the "typical healthy individual" (i.e. excluding residual variability and between-subject variability), with the following covariate inputs: Age = 51 years, Fed = 1, healthy volunteer = 1, other disease state = 0, IA disease state = 0, Chinese = 0. Below are the results of the NCA for single dose simulations:

**Supplementary Table 4: NCA Analysis of 300 mg Single-Dose DRT in Typical Simulated Individuals**

| DOSE (mg) | Weight (kg) | AUC_inf (ng*h/mL) | CMAX (ng/mL) | TMAX (h) | HL (h) | CL_f_obs (L/h) | Vz_f_obs (L) | HL GMR[1] |
|---|---|---|---|---|---|---|---|---|
| **300** | **70** | **43,801** | **969.9** | **6** | **28.2** | **6.8** | **278.8** | **1.00** |
| 300 | 100 | 36,019 | 687.4 | 6 | 38.4 | 8.3 | 461.9 | 1.36 |
| **300** | **120** | **32,629** | **579.3** | **6** | **45.2** | **9.2** | **599.6** | **1.60** |
| 300 | 140 | 30,028 | 501.8 | 6 | 51.7 | 10.0 | 745.0 | 1.83 |
| 300 | 160 | 27,952 | 442.9 | 6 | 58.0 | 10.7 | 898.4 | 2.06 |
| 300 | 180 | 26,245 | 396.5 | 6 | 64.2 | 11.4 | 1058.7 | 2.28 |

[1]HL GMR calculated relative to 70 kg patient.

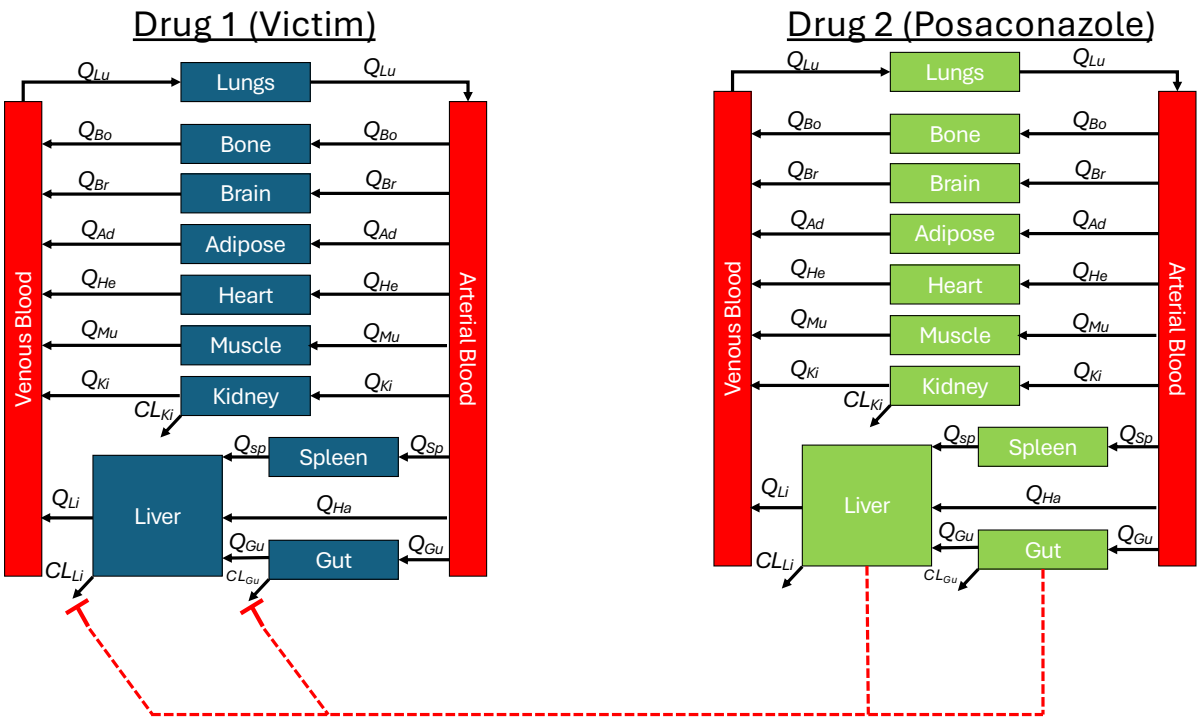
References:


1. Chow CR, Harmatz JS, Ryan MJ, Greenblatt DJ. Persistence of a Posaconazole-Mediated Drug-Drug Interaction With Ranolazine After Cessation of Posaconazole Administration: Impact of Obesity and Implications for Patient Safety. *The Journal of Clinical Pharmacology*. 2018;58(11):1436-1442. doi:10.1002/jcph.1257

2. Greenblatt DJ, Harmatz JS, Ryan MJ, Chow CR. Sustained Impairment of Lurasidone Clearance After Discontinuation of Posaconazole: Impact of Obesity, and Implications for Patient Safety. *Journal of Clinical Psychopharmacology*. Published online May 2018:1. doi:10.1097/JCP.0000000000000892

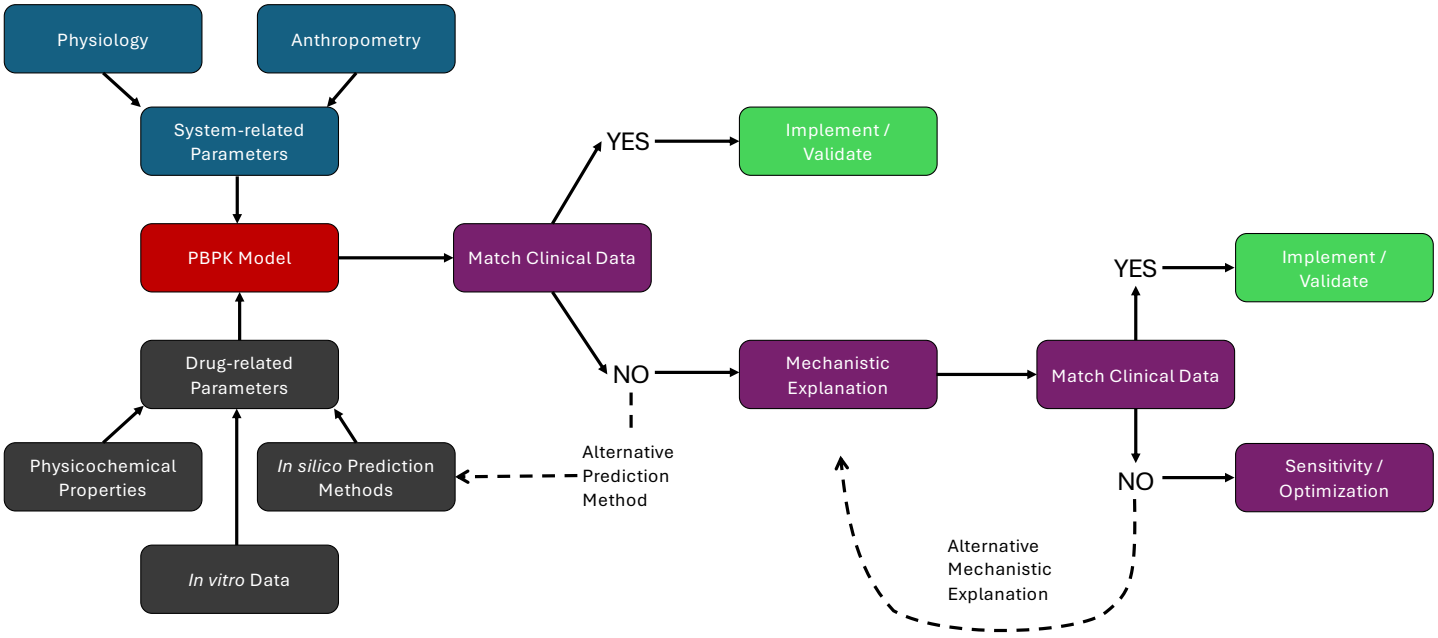
3. Noxafil-H-C-610-II-0062: EPAR – Assessment Report – Variation. European Medicines Agency. 16 September 2021. Available from: https://www.ema.europa.eu/en/documents/variation-report/noxafil-h-c-610-ii-0062-epar-assessment-report-variation_en.pdf.

# Supplementary Figure 1: PBPK Model Structure




Q = blood flow, CL = clearance. Ha = hepatic artery. Ad, Bo, Br, Gu, He, Ki, Li, Lu, Mu, and Sp refer to adipose, bone, brain, gut, heart, kidneys, liver, lungs, muscle, and spleen, respectively.

# Supplementary Figure 2: PBPK Model Workflow




**Posaconazole Clinical Data:**

**Calibration:**
- Kersemaekers et al. 2015 (200 mg, 250 mg, and 300 mg IV)

**Verification & Validation:**
- Kersemaekers et al. 2015 (50 mg, 100 mg IV)
- BOW Studies (assessing half-life)
  - Normal weight
  - Obesity

**Ranolazine Clinical Data:**

**Calibration:**
- BOW-001 Study Day 1

**Verification & Validation:**
- Moss et al. 2008
- Tan et al. 2013

**Lurasidone Clinical Data:**

**Calibration:**
- BOW-002 Study Day 1

**Verification & Validation:**
- Hu et al. 2017
- Findling et al. 2015

**DDI Kinetics Clinical Data:**

**Calibration:**
- BOW-001 (ranolazine)
- BOW-002 (lurasidone)

# 1 Model Equations

**General PBPK model equations:**

Non-eliminating compartment:

$$\frac{dA_T}{dt} = Q_T(C_A - \frac{C_T}{\frac{Kp_T}{BP}}) \tag{1}$$

Eliminating compartment:

$$\frac{dA_T}{dt} = Q_T(C_A - \frac{C_T}{\frac{Kp_T}{BP}}) - (CL_T + (\frac{V_{max,T}}{K_m + \frac{C_T}{\frac{Kp_T}{BP}}})).\frac{C_T}{\frac{Kp_T}{BP}} \tag{2}$$

Arterial blood compartment:

$$\frac{dA_A}{dt} = Q_{Lu}(\frac{C_{Lu}}{\frac{Kp_{Lu}}{BP}} - C_A) \tag{3}$$

Venous blood compartment:

$$\frac{dA_V}{dt} = \sum_{T \neq Lu} (Q_T.\frac{C_T}{\frac{Kp_T}{BP}}) - Q_{Lu}.C_V \tag{4}$$

Lung compartment:

$$\frac{dA_{Lu}}{dt} = Q_{Lu}(C_V - \frac{C_{Lu}}{\frac{Kp_{Lu}}{BP}}) \tag{5}$$

where:

- $A$, $C$, $Q$, $CL$, $V_{max}$, $K_m$, $Kp$, and $BP$ refer to drug amount, concentration, blood flow rate, linear clearance, maximum rate for nonlinear clearance, Michaelis-Menten constant, partition coefficient, and blood to plasma concentration ratio, respectively.
- The subscripts $T$, $A$, $V$, and $Lu$ refer to tissue, arterial blood, venous blood, and lung compartments, respectively.

**Absorption of Ranolazine:**

$$\frac{dA_{depot}}{dt} = -k_{rel} * A_{depot} \tag{6}$$

$$\frac{dA_{lumen}}{dt} = k_{rel} * A_{depot} - k_d * F_a * A_{lumen} \tag{7}$$

where:

- $A_{depot}$ and $A_{lumen}$ refer to the amount of ranolzaine in the depot and gut lumen compartments, respectively.

- $k_{rel}$, $k_d$, and $F_a$ refer to ranolazine release, disappearance from gut lumen rate constants, and fraction absorbed, respectively.

**CYP3A4 enzyme kinetics with posaconazole DDI :**

$$\frac{dE_T}{dt} = R_{0,T} - k_{deg,T} * E_T - \frac{k_{inact} * C_{T,posa}}{KI + C_{T,posa}} \tag{8}$$

$$E_{0,T} = \frac{R_{0,T}}{k_{deg,T}} \tag{9}$$

$$CL_T = CL_{0,T} * \frac{E_T}{E_{0,T}} \tag{10}$$

where:

- $E$, $C_{posa}$, and $CL$ refer to CYP3A4 enzyme amount, posaconazole concentration, and victim drug clearance, respectively.
- $E_0$ and $CL_0$ refer to baseline CYP3A4 amount and victim baseline clearance, respectively.
- $k_{deg}$, $k_{inact}$, and $KI$ refer to enzyme degradation, inactivation by posaconazole rate constants, and dissociation constant between enzyme and posaconazole.
- the subscript $T$ refers to the eliminating tissue.