A Joint Concentration-Response Model for ABPM Measurements of Systolic and Diastolic Blood Pressure

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INTRODUCTION

An experimental drug, LY, was being evaluated for use as a chronically-administered once weekly subcutaneous injection. Dose-dependent increases in diastolic blood pressure were observed in early clinical studies, although these studies were not adequately powered to determine statistical or clinical significance.

Given the need to fully characterize the cardiovascular safety of new therapies, Lilly prospectively assessed the effects of Phase 2 dose levels of LY on blood pressure using ambulatory blood pressure monitoring (ABPM).

OBJECTIVES

- To develop an exposure-response model characterizing the relationship between LY concentration and ABPM of systolic (SBP) and diastolic (DBP) blood pressure
- To predict blood pressure responses to LY under alternative dosing regimens
- To develop relevant priors to facilitate analysis using sparse data from subsequent Phase 3 trials

METHODS

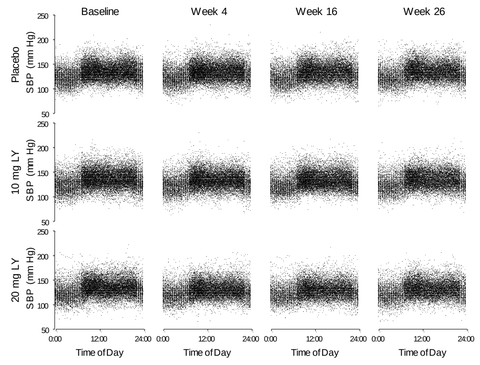
Study Design

A multicenter, randomized, double-blind, parallel-arm, placebo-controlled study was conducted to evaluate the effects of LY on blood pressure using ABPM. A total of 755 patients were randomized to placebo, 10 mg or 20 mg LY. ABPM was performed prior to randomization, and at 4, 16, and 26 weeks. Five plasma samples were collected from each patient for determination of LY concentrations.

ABPM Measurements

Blood pressure and heart rate were measured at 20 minute intervals during the day (7:00 - 22:00) and 30 minute intervals during the night (22:00 - 7:00). A total of 188,177 ABPM measurements were collected from 743 patients.

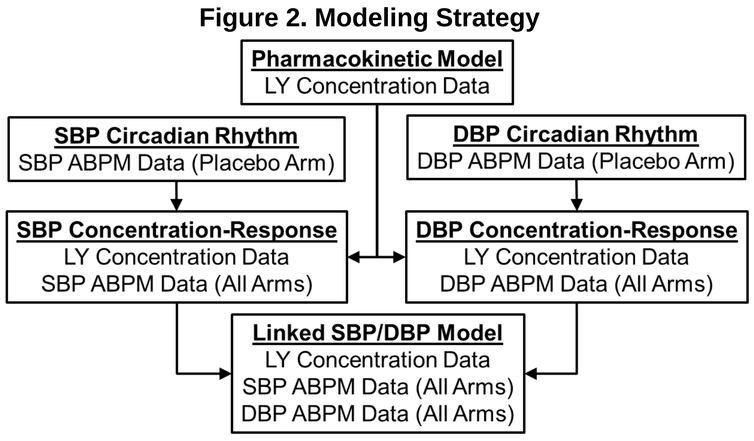
Figure 1. ABPM of Systolic Blood Pressure



Modeling Strategy

A stepwise approach was used for modeling the very large ABPM dataset. First, a pharmacokinetic model was established. Circadian rhythm models were developed for SBP and DBP, using only placebo data. Exposure-response models were developed for SBP and DBP, using data from both placebo and LY-treated patients. Finally, all data was combined to construct the linked model. All analyses were performed using NONMEM 7.2.

Figure 2. Modeling Strategy



Pharmacokinetic Model

A two-compartment model with first-order absorption was applied to the concentration data, based on a model previously developed using data from an absolute bioavailability study. Inter-patient variability was estimated on clearance and central compartment volume. Increasing LY dose and body weight both decreased the extent of absorption.

SBP/DBP Circadian Rhythm Models

- Approximately 60,000 observations from 234 patients were available from placebo-treated patients for SBP and DBP
- The circadian rhythm for SBP and DBP was modeled using a sum of cosine functions with periods of different lengths

$$BP = E_0 \cdot \left[1 + Amp_{24} \cdot \cos\left(\frac{2\pi \cdot (TOD - Phase_{24})}{24}\right) + Amp_{12} \cdot \cos\left(\frac{2\pi \cdot (TOD - Phase_{12})}{12}\right)\right]$$

Amp = Maximum Change in BP; Phase = Phase Shift; TOD = Time of Day

SBP/DBP Covariate Analyses

- Circadian rhythm models were first developed using First Order Conditional Estimation with interaction and only inter-patient variability to:
  - Avoid Monte Carlo noise in the objective function
  - Maintain shorter run-times
- Stepwise covariate analysis was then performed on:
  - Demographics: age, body weight, body mass index, sex, ethnic origin, geographic region, and smoking status
  - Patient status: hypertensive status, baseline SBP/DBP
  - Concomitant medications: ACE inhibitors, angiotensin receptor blockers, beta blockers, calcium channel blockers, and diuretics
- Importance Sampling was then used for estimation of inter-occasion variability in final covariate models.

SBP/DBP Concentration-Response Models

- Approximately 177,000 observations from 696 patients were available from placebo- and LY-treated patients for both SBP and DBP
- A sequential approach was taken, with pharmacokinetic parameters fixed, and concentrations included in the dataset
- Direct response and effect compartment models were evaluated, to account for potential hysteresis

$$BP = E_0 \cdot \left[1 + Cos_{24} + Cos_{12} + \ldots\right] + \frac{Emax \cdot C^{\gamma}}{EC_{50}^{\gamma} + C^{\gamma}}$$

C = Concentration in plasma or at effect site; Cos_N = Cosine of period N

Linked Blood Pressure Model

- All concentration, SBP, and DBP data was combined
- Correlation in inter-patient and inter-occasion variability between SBP and DBP was evaluated for all parameters
- SAEM estimation method was used.

Model Evaluation

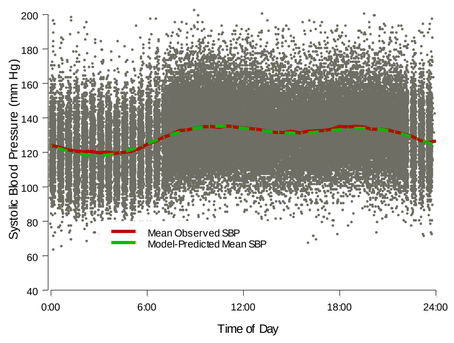
- The final model was qualified using bootstrap and visual predictive checks (VPC). The VPC included SBP and DBP, as well as the derived variables mean arterial pressure (MAP) and pulse pressure (PP).

RESULTS

Circadian Rhythm

- SBP and DBP were both well-described by a sum of cosines with 24- and 12-hour periods
- While separate amplitude parameters were used for SBP and DBP, phase parameters were shared.

Figure 3. Circadian Rhythm of Systolic Blood Pressure



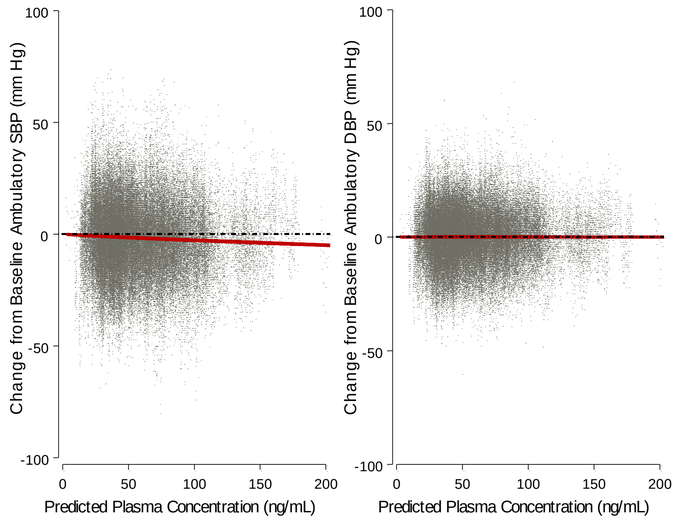
Covariate Analyses

- Consistent with physiology, baseline SBP was found to increase with age
- Gender influenced baseline DBP, with males having 6.6% higher values. Additionally, North American patients had 2.6% lower baseline DBP.

Exposure-Response

- SBP was found to decrease linearly with increasing LY concentration. No hysteresis was observed
- No relationship was found between DBP and concentration.

Figure 4. Concentration-Response Relationship for Systolic and Diastolic Blood Pressure



Dotted line represents no change. Red line represents model-predicted concentration response relationship.

Final Linked SBP/DBP Model

- Covariance estimated for SBP/DBP baselines, amplitudes, and phases in both inter-patient and inter-occasion variability.

Linked SBP/DBP Model Parameter Estimates

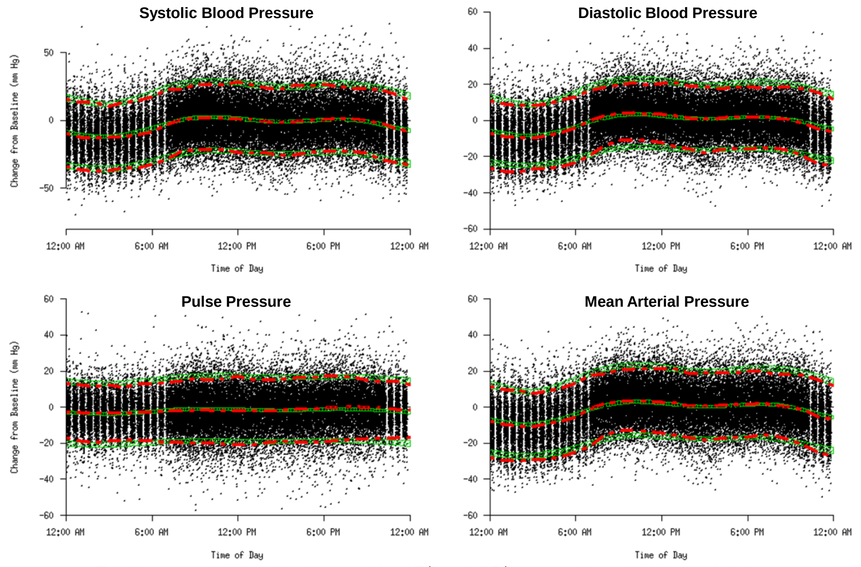
Parameter Description	Population Estimate (%SEE)	Inter-Subject Variability (%SEE)	Inter-Occasion Variability (%SEE)
Baseline SBP (mm Hg)	129 (0.308)	7.47% (3.48)	4.49% (1.08)
correlation coefficient	---	0.599 (3.86)	0.856 (0.698)
Baseline DBP (mm Hg)	73.5 (0.644)	8.48% (3.74)	4.75% (1.14)
SBP 24 Hour Amplitude (fraction)	0.0510 (3.78)	50.5% (2.99)	47.4% (2.25)
correlation coefficient	---	0.727 (2.61)	0.770 (1.69)
DBP 24 Hour Amplitude (fraction)	0.0774 (3.05)	40.5% (3.55)	37.9% (2.31)
SBP 12 Hour Amplitude (fraction)	0.0355 (2.70)	38.5% (4.22)	40.2% (3.43)
correlation coefficient	---	0.788 (3.07)	0.735 (2.64)
DBP 12 Hour Amplitude (fraction)	0.0488 (2.40)	33.9% (4.51)	38.2% (3.63)
24 Hour Phase (hour)	14.0 (0.907)	17.9% (4.01)	13.1% (4.10)
correlation coefficient	---	0.361 (9.16)	0.228 (15.0)
12 Hour Phase (hour)	8.70 (0.676)	14.3% (5.45)	13.2% (4.50)
Effect of Age on SBP Baseline (power)[a]	0.174 (7.59)	---	---
Effect of Gender on DBP Baseline (%)	6.58 (10.1)	---	---
Effect of Region on DBP Baseline (%)	-2.60 (23.0)	---	---
SBP Concentration-Response (mm Hg/ng/mL)	-0.0546 (13.0)	91.0% (32.6)	---
Scaling Exponent for Concentration (power)	0.854 (2.92)	15.1% (FIXED)	---
Residual Error			
SBP (%)		8.14 (0.0946)	
correlation coefficient		0.603 (0.251)	
DBP (%)		11.0 (0.161)	

[a]SBP = 129*(age/56)0.174. SEE = standard errors of estimation

Model Evaluation

- Bootstrap and VPCs confirmed the suitability of the model.

Figure 5. VPC for 10 mg Dose Group: Change from Baseline

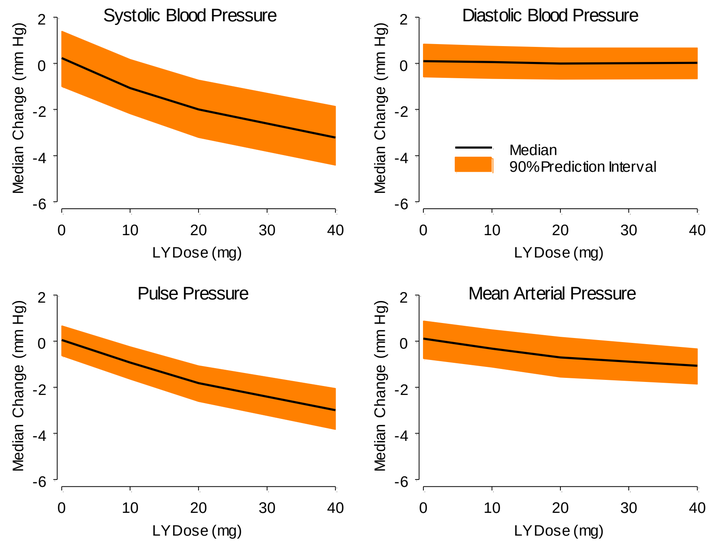


Red lines correspond to the median, 5th and 95th percentiles of observed data. Green shaded regions correspond to model-predicted 90% confidence intervals

Simulation of Alternative Dosing Regimens

- The model can be used to simulate the expected change from baseline in ABPM values for alternative dosing regimens.

Figure 6. Expected Blood Pressure Response to Once Weekly Dosing Regimens



Priors for Phase 3 Analyses

- The final linked model established priors for SBP and DBP parameters in the target patient population
- Including correlation between SBP and DBP parameters allows the model to leverage the maximum amount of information from sparse Phase 3 datasets
- Priors were successfully implemented in the Phase 3 analysis, allowing characterization of blood pressure response in the Phase 3 patient population.

CONCLUSIONS

- LY concentration is associated with a slight decrease in SBP, well described by a linear model
- The final linked concentration-response model described SBP and DBP response to LY very well, as shown by the VPC. The relationship between SBP and DBP was also well characterized, as shown by the VPC of MAP and PP
- The model provided an understanding of blood pressure response to LY therapy, and allows prediction of responses to LY in alternative dosing regimens.

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