Poster Number: 018 Table 1. Population PK Parameter of Metformin from Base and Covariate Model

		Base Model (-2LL = 600.3)		Covariate Model (-2LL = 530.7)	
Parameters	Units	Estimates	CV%	Estimates	CV%
tvKa	1/h	0.39	22.1	0.39	11.7
tvV	L	1,500	108.1	1,993	3.9
tvCL	L/h	50.0	96.2	55.1	2.0
dKad (surgery)				-0.4	-7.7
dVd (surgery)				-0.9	-0.2
dCLd (CLcr)				1.0	6.3

Interpretation, Conclusion or Significance: A population PK model of metformin in patients undergoing GBS was developed for the first time. This model will be useful in predicting plasma concentrations of metformin pre- and post-surgery in patients undergoing GBS. The model demonstrates that surgery causes a significant decrease in Ka and Vd/F of metformin post-surgery. The effect on Ka might be due to the decrease in the surface area available for absorption in the intestine after surgery. On the other hand, the effect on Vd/F might be due to the loss of lean body mass in addition to the loss of fat mass post-surgery.

Poster Number: 019

Confirmation of the Cardiac Safety of OBE022 in a Phase 1 Study in Healthy Subjects Using Intensive ECG Assessments and the Effect of a Meal on QTc to Show Assay Sensitivity

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Statement of Purpose, Innovation or Hypothesis: A new orally-active molecule with myometrial selectivity and competitive Prostaglandin F (FP) receptor antagonist properties is being developed to reduce uterine contractions during pre-term labor. The aim of this Phase 1 study was to evaluate the effect of OBE022 following multiple doses on the QT interval in healthy post-menopausal women using the effect of a meal on QTc to prove assay sensitivity.

Description of Methods and Materials: In this study, 23 healthy post-menopausal women were randomly assigned to one of three dose groups or placebo (3:1 ratio). On Day 1 a high-fat breakfast was served 30 min before dosing. Breakfast contained 784.8 kcal with an approximated ratio of 16.6% protein, 31.6% carbohydrate and 51.8% fat. On Days 3 and 9, the OBE022 was administered in the fasted state and first meal was lunch at 4 h post-dose. Lunch contained 606.6 kcal with an approximated ratio of 20.9% protein and 75.8% carbohydrate to 3.3% fat. The effect of the IMP on QTcF was assessed using concentration-response modeling.

Data and Results: The concentration-response analysis showed an absence of any QTc prolonging effect at the doses tested. The two-sided 90% confidence interval for the predicted effects of the OBE022 and its main metabolite at the geometric mean C_{max} of each of the dose groups was completely below the threshold of regulatory concern. The sensitivity of this study to detect small changes in the QTc interval was confirmed by demonstrating a significant shortening of QTcF on Days 1, 3 and 9 after a standardized meal. On Day 1, the change from the average of 3 pre-dose, pre-meal triplicate ECGs was used while for Days 3 and 9, the average of the 3 post-dose, pre-meal ECGs were used.

Interpretation, Conclusion or Significance: This study shows that the OBE022 has no QTc-prolonging effects. The observed food effect confirms the validity of the assay in all days tested and is in the range of values observed in the literature. The method was shown to be specific when both the change from pre-dose, pre-meal and also change from pre-meal, post-dose are evaluated.

Clinical Trials & Human Pharmacology

Poster Number: 020

The 24-hour Profile of Moxifloxacin Effect on QTc: A Reflection of Diurnal Variations

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Statement of Purpose, Innovation or Hypothesis: Moxifloxacin is a broad-spectrum fluoroquinolone antibiotic with a well-documented and consistent QT prolongation effect, used in many TQT studies to demonstrate the sensitivity of the assay. The pharmacokinetic (PK)-QTc analysis points to a linear relationship between the plasma concentration of moxifloxacin and the increase in QTc interval from baseline. However, hysteresis effects have been attributed to environmental factors. This study aims to define the timecourse of the effect of moxifloxacin on the QT interval with continuous Holter data in order to understand the distribution of the responses to moxifloxacin.