PII-16

PK AND PD OF ESCALATING, SINGLE IV DOSES OF A SYNTHETIC ALLOSTERIC HEMOGLOBIN (Hb) MODIFIER, RSR13, IN PATIENTS WITH STABLE EFFORT ANGINA. J. Venitz, MD, PhD,[1] J.F. Liard, MD,*[2] J. Hackman, PhD,*[2] Department of Pharmaceutics, Virginia Commonwealth University,[1] Richmond, VA; Allos Therapeutics Inc.,[2] Denver, CO.

RSR13 allosterically modifies Hb to decrease O_2-affinity. In this placebo-controlled, double-blind phase Ib study, single doses of 50, 75 or 100 mg/kg were given as IV infusions over 90 minutes to 16 patients with stable effort angina. Concentrations of RSR13 were determined by HPLC over 48 hrs in plasma (C_p), erythrocytes (C_{RBC}) and urine. PD effects were measured as shift (P_{50}) and change in slope (n) of the *ex-vivo* O_2-equilibrium curve of whole blood.

Noncompartmental PK analysis revealed nonlinear systemic PK: CL_{tot} decreased from 49 to 30 ml/min with f_e decreasing from 60 to 40% suggesting both saturable renal tubular secretion and nonrenal elimination pathways. Vd_{ss} was constant at 0.2 L/kg, while the terminal $t_{1/2}$ increased from 4.1 to 9.2 hrs. In general, C_p and C_{RBC} were similar; AUC_{RBC} increased supra-proportionally with dose. The AUC_{RBC}/AUC_p ratio increased from 0.74 to 1.04 suggesting saturable plasma protein binding. Both PD effects increased with dose, and were a linear function of the RBC concentrations.

(Partial Support: Allos Therapeutics, Denver, CO.)

PII-17

EFFECT OF CLEMASTINE ON THE ECG IN HEALTHY VOLUNTEERS. S.U. Yasuda, MS, PharmD, M. Ndey, MD,* R.L. Woosley, MD, PhD, Depts of Pharmacology and Medicine, Georgetown U Med Ctr, Washington, DC.

Introduction: Clemastine is an over-the-counter antihistamine that at concentrations greater than 5 μM produces potassium channel blockade in *in vitro* models. Potassium channel blockade can lead to the potentially lethal arrhythmia, torsades de pointes. The purpose of this study was to evaluate the effect of clemastine on the ECG in healthy volunteers.

Methods: 19 healthy volunteers (10 men, 9 women) were given clemastine 2.68 mg tid or placebo in a randomized, crossover study. After 3 days of chronic administration, an ECG was performed at fixed times following the last dose of study medication. QT intervals were marked manually, measured using a bitpad, and checked manually in a blinded manner. QTc was corrected for heart rate using Bazett's correction. **Results:** No differences between clemastine and placebo were observed in RR interval. For QTc, no difference was observed between clemastine and placebo for the total study population. However, in women the mean QTc over the last 8-hour dosing interval was significantly greater ($p<0.05$) for clemastine (420±21, mean±SD) compared to placebo (411±19, mean±SD). **Conclusions:** A commonly used dose of clemastine prolonged QTc in women and may increase risk of arrhythmia in susceptible patients.

PII-18

PK-PD RELATIONSHIP OF THE EFFECTS OF ARGATROBAN ON HAEMOSTASIS IN HEALTHY YOUNG VOLUNTEERS. D. Garrigou,* PhD,[1] C. Dubruc,* PhD,[1] C. Thuillez, MD,*[2] L. Bergougnan,* MD,[1] J.P. Thenot,* PhD,[1] Synthélabo Recherche,[1] Chilly Mazarin, France; C.H.U. Rouen Service de Pharmacologie Clinique, Rouen,[2] France.

Argatroban is a synthetic inhibitor of thrombin active site. Its tolerability, pharmacokinetics and effects on hemostases have been studied in 9 healthy young volunteers given 2 and 4 μg/kg/min 4h-IV infusions. Mean argatroban plasma concentrations at the end of the infusion were 472 and 908 ng/mL respectively. Mean maximum increases (ratio vs basal values) were 2.0 and 2.3 for aPTT and 3.2 and 4.0 for ECT. Plasma concentrations were fitted by non linear least squares regression analysis (Gauss-Newton algorithm) with WinNonlin software. The best fit was obtained according to a 2-compartment model with $1/\hat{y}$ weighting. An Emax direct model was found to best describe the pharmacodynamic relationship between coagulation parameters and plasma concentrations. Emax, EC50 and E0 mean values were 79 sec, 524 ng/mL and 30 sec for aPTT and 142 sec, 846 ng/mL and 20 sec for ECT. The smaller coefficients of variation were obtained for ECT. Using this PK-PD model, it is possible to predict the time course of the pharmacodymic effect following both IV dosing. This model may be applied to other routes of administration.

PII-19

IMPACT OF CLINICAL PHARMACIST-BASED INTERVENTION ON OUTCOMES IN CHF. Aileen B. Luzier, PharmD,* Brad Robison, MD,* Stephen G. Feuerstein,* Jerome J. Schentag, PharmD, Joseph L. Izzo, MD, School of Pharmacy, School of Medicine & Biomedical Sciences, SUNY at Buffalo & Millard Fillmore Health Systems, Buffalo, NY.

We investigated the impact of pharmacologic intervention on outcomes in CHF. We developed a multi-disciplinary disease management program including a clinical pharmacist who assessed appropriateness of drug therapy based on the AHCPR guidelines. All patients had systolic dysfunction defined by echocardiography. For patients on suboptimal therapy, recommendations were made to optimize their drug regimen. Concerted efforts were made to initiate ACE inhibitor therapy and titrate doses to those recommended in the AHCPR guidelines. Of the 110 patients enrolled, treatment was suboptimal in 75% on initial assessment. Principal reasons for suboptimal therapy were failure to use ACE inhibitor (21%) and inadequate dose of ACE inhibitor (54%). In suboptimal cases, clinical pharmacist intervention resulted in 51 cases where therapy was changed to meet the guidelines. In 31 patients, physicians declined pharmacist intervention and patients remained on suboptimal therapy. Optimizing drug regimens lead to improved outcomes for the 90-day period post-discharge:

Patient Group	Charges (mean, SE)	Readmission
Appropriate initial therapy	$2444 (987)	4 (14%)*
Therapy changed to meet guidelines	$3297 (986)	4 (8%)*
Remained on suboptimal therapy	$7024 (2263)	9 (29%)

*$p<0.05$ vs remained on suboptimal therapy

Conclusions: Assessment of drug therapy is important in disease management programs and can improve patient outcomes. Intervention by a clinical pharmacist is useful in those cases where treatment regimens did not follow accepted guidelines.