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Abstracts

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1708878

Evaluation of Blockade of Reconsolidation of Cocaine-craving Responses by Propranolol

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Statement of Purpose, Innovation or Hypothesis: Relapse to drug misuse may follow exposure to drug cues, presumably because the cues activate Pavlovian associations that may be subject to reconsolidation each time they are recalled. Disruption of reconsolidation by propranolol in a memory-reactivation session may provide enduring protection against cue-induced craving and relapse. We evaluated the effects of propranolol, a beta-blocker, on reconsolidation of cue-induced drug cravings in methadone-maintained cocaine users.

Description of Methods and Materials: Healthy, cocaine users receiving methadone maintenance (n = 33) were each interviewed to develop personalized auditory script/cue sets based on a specific cocaine-use memory and neutral event. In a reactivation/intervention session, propranolol 40 mg or placebo (random assignment, double-blind) was administered orally 2 hrs before presentation of the script/cue sets. Responses to re-exposure to the script/cue sets were tested 1 and 5 weeks after the reactivation/intervention session. Ongoing drug use was monitored via urine screens and self-report in twice-weekly visits.

Data and Results: One week after the propranolol/placebo intervention, the cocaine-craving script increased VAS ratings of craving in both groups, $F(1,31) = 6.10$, $p < .02$, with mean change scores of +5.41 (SEM 2.12) for the cocaine script and −1.18 (SEM 2.43) for the neutral script. Five weeks after the intervention, the cocaine-craving script still tended to increase VAS ratings of craving in both groups, $F(1,29) = 3.35$, $p < .08$, though the specificity of this effect was dampened, with mean change scores of +8.39 (SEM 2.54) for the cocaine script and +3.89 (SEM 2.72) for the neutral script. Contrary to our hypothesis, the propranolol group was especially reactive to the cocaine script both acutely after propranolol administration and during the subsequent test sessions, though this was not reflected in significant effect of Group or Group x Script interactions. There were no significant group differences in percentage of cocaine-positive urine specimens.

Interpretation, Conclusion or Significance: Our results do not support the use of propranolol for disruption of cue-induced cocaine craving under the conditions tested in our study though better results with higher doses of propranolol and more intervention sessions are possible.

This research was supported by the Intramural Research Program, National Institute on Drug Abuse (NIDA), National Institutes of Health.

1709382

Safety and Tolerability of Aripiprazole Once-Monthly in Adults With Schizophrenia Stabilized on Atypical Oral Antipsychotics Other Than Aripiprazole

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Encore Presentation: *25th Annual US Psychiatric and Mental Health Congress, San Diego, CA, USA; November 8–11, 2012; abstract available at: http://www.psychcongress.com/posters/open-label-safety-and-tolerability-study-once-monthly-aripiprazole-treatment-initiation.*

Statement of Purpose, Innovation or Hypothesis: To evaluate the safety and tolerability of aripiprazole once monthly (ARI-OM), an extended-release injectable suspension, initiated in patients stabilized on oral antipsychotics other than aripiprazole.

Description of Methods and Materials: Patients with schizophrenia were stabilized for ≥14 days on oral risperidone, olanzapine, quetiapine, or ziprasidone before administration of ARI-OM 400 mg. Oral antipsychotics were continued for up to 14 days after the initiation of ARI-OM. Safety and tolerability of a single ARI-OM dose were assessed, including adverse events (AEs); extrapyramidal symptoms (EPS) using 3 different scales; suicidality using the Columbia-Suicide Severity Rating Scale (C-SSRS); clinical laboratory measures; and weight change.

Data and Results: 60 patients initiated ARI-OM 400 mg while continuing oral risperidone (n = 24), quetiapine (n = 28), ziprasidone (n = 5) or olanzapine (n = 3). Symptoms remained stable, as assessed by the Positive and Negative Syndrome Scale. AEs were mild and dose-independent. Treatment-emergent (TE) AEs (≥5%) were fatigue, injection-site pain, and restlessness (8.3% each) for risperidone; insomnia (10.7%), dystonia (7.1%), injection-site pain (7.1%), toothache (7.1%), and increased blood creatinine phosphokinase (7.1%) for quetiapine; and muscle spasm, tooth abscess, and toothache (20% each) for ziprasidone. Olanzapine-treated patients did not report any AEs. TE EPSs were similar across groups (<5%). There were no unusual changes in C-SSRS scores, weight, lab values, or fasting metabolic parameters.

Interpretation, Conclusion or Significance: ARI-OM 400 mg may offer a relatively well-tolerated maintenance treatment option for patients with schizophrenia. ARI-OM 400 mg was not associated with unexpected safety-related outcomes while patients transitioned from oral atypical antipsychotic therapy.

This study was supported by Otsuka Pharmaceutical Development and Commercialization, Inc. and H. Lundbeck A/S.

1709413

Comparison of Three Titration Algorithms for Initiation of Basal Insulin in Patients With Type 2 Diabetes Mellitus

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Encore Presentation: *Dailey G; Aurand L; Stewart J; Ameer B; Zhou R. Comparison of Three Titration Algorithms for the Initiation of Basal Insulin in Patients with Type 2 Diabetes Mellitus. Diabetologia. 2012;55(Suppl 1):S383 (abstract 935).*

Statement of Purpose, Innovation or Hypothesis: To achieve target fasting plasma glucose (FPG) in patients with type 2 diabetes mellitus (T2DM), many basal insulin titration algorithms have been studied and it may be difficult to choose one. This pooled analysis of patient-level data compared endpoints from studies using different algorithms for initiation and intensification of insulin glargine in insulin-naïve patients with T2DM.

Description of Methods and Materials: Data were pooled from 8 randomized controlled trials (RCT) that added insulin glargine to OADs at 10U starting dose. Change from baseline endpoint variables were analyzed using a mixed model with algorithm as a factor and corresponding baseline measurement as covariate.

Data and Results: Algorithm 1 (n = 163; age 57, 66% men) required 1U daily when FPG > target; algorithm 2 (n = 117; age 59, 62% men) 2U every 3 days when FPG > target; algorithm 3 (n = 1100; age 57, 54% men) used treat-to-target, increasing 2-8U weekly based on 2-day mean FPG. At baseline, there were differences in FPG and A1C levels. After adjusting for baseline measurements, algorithm 2 had significantly greater change in A1C than did 1. Algorithm 3 tended towards more confirmed hypoglycemia, and in all groups the incidence of severe hypoglycemia was low, ranging 0–1.5%. Final insulin doses were 0.43 U/kg, 0.60 U/kg and 0.44 U/kg for algorithms 1, 2 and 3; with significantly higher doses for algorithm 2 vs 1 and 3. Baseline OAD therapy use differed across groups; those receiving metformin and a sulfonylurea (SU) made up 51%, 70% and 71% of algorithms 1, 2 and 3.

Interpretation, Conclusion or Significance: These data suggest simpler titration algorithms (1 and 2) achieved similar glycemic control vs more complex algorithms (3) with less confirmed hypoglycemia. This may assist the choice of algorithm for intensification of basal insulin, but needs validation with a RCT. Study funded by Sanofi US, Inc.

1709425

Individual and Regional Variability of Postprandial Hyperglycemic Patterns

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Encore Presentation: *Reid T; Shaefer C; DiGenio A; Vlajnic A; Zhou R; Ameer B; Riddle MC. Individual and regional variability of postprandial hyperglycemic patterns. Keystone Symposia: Diabetes - New Insights into Mechanism of Disease and its Treatment (J6). 2013; Poster 3010. January 27 – February 1, 2013, Keystone, Colorado USA*

Statement of Purpose, Innovation or Hypothesis: If adding basal insulin to oral therapy for type 2 diabetes (T2DM) does not maintain A1C <7.0%, treatment of postprandial hyperglycemia (PPHG) is needed. Individual patterns of hyperglycemia may determine treatment effectiveness. To define these, we studied self-monitored blood glucose (SMBG) profiles from 6 randomized controlled trials where insulin glargine or comparator insulin/oral therapy was added to prior therapy and titrated for 24 weeks (N = 1699).

Description of Methods and Materials: Patients selected had T2DM, A1C ≥7.0%, and 7-point SMBG data at wk24 (n = 494); Mean values: age 60 yrs, T2DM duration 9.6 yrs; wk24 BMI 30.7 kg/m^2, insulin dose 0.45 U/kg, A1C 7.8%, fasting glucose 126 mg/dL. PPHG was studied in 4 regions: Germany (G; n = 225), other EU (EU; n = 137), Canada (C; n = 69), USA (n = 63).

Data and Results: At wk24, mean SMBG values 2h post-breakfast (B), lunch (L), and dinner (D) averaged 179, 174, and 190 mg/dL. BG increments post-B, L, and D averaged 57, 34, and 41 mg/dL. Characteristics of patients with highest postprandial glucose (PPG) and largest BG increment from pre- to postprandial were similar. D was the meal with the highest PPG (G 43%, EU 42%, C 42%, and USA 51%) and B the largest BG increment (G 48%, EU 43%, C 49%, and USA 41%). Post-D BG at wk24 was significantly higher in USA and C vs G ($P = 0.0004$ and $P = 0.0266$) and in USA vs EU ($P = 0.0130$). Wk24 BG increment post-B was significantly higher in USA and C vs G ($P = 0.0001$ and $P = 0.0239$) and in USA vs EU ($P = 0.0071$).

Interpretation, Conclusion or Significance: Individual postprandial patterns differ widely; similarity of clinical characteristics and geographical variability suggest differing eating behaviors underlie such patterns. Further analysis of regional differences in PPHG by individual meal time is warranted. Study funded by Sanofi US, Inc.

1710334

Characterization of HCV NS3 Variants That Emerged During Virologic Breakthrough and Relapse From Faldaprevir Phase II SILEN-C2 Study in PegIFN/RBV Treatment-experienced Patients

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Encore Presentation: *EASL 2012 Poster presentation. Abstract published in: Journal of Hepatology Vol. 56;Supplement 2, Page S469*

Statement of Purpose, Innovation or Hypothesis: SILEN-C2 evaluated faldaprevir + PegIFNα-2a + ribavirin (PR) in GT1 patients non-responsive to previous PR (relapsers excluded). Treatments included 240 mg QD with/without 3-day PR lead-in or 240 mg BID with 3-day PR lead-in, plus PR for 24W. This study aimed to characterize viral variants in non-SVR patients.

Description of Methods and Materials: HCV NS3/4A baseline changes in non-SVR patients were identified by population sequencing. Viral breakthrough (BT) is HCV rebound on-treatment ≥1 $\log_{10}$ from nadir, or increase to ≥100 IU/mL if nadir undetectable. Post-treatment rebound includes relapse and incomplete viral response (ICVR).

Data and Results: BT occurred in 23.6% (68/288) of patients receiving faldaprevir; GT1a viruses (n = 37) largely encoded R155 mutants and GT1b viruses (n = 30) encoded only D168 changes. Median time for faldaprevir BT was 30 days. Lower BT rates occurred with faldaprevir BID (17.1%, 12/70), where both GT1a and 1b virus encoded only D168; overall efficacy was off-set by a higher discontinuation rate in the BID group. BT during PR therapy following faldaprevir occurred in 5.6% (16/288) of patients, most with R155K mutants (12/16). ICVR and relapse rate from all faldaprevir-treatment arms was 33.7% (97/288) and characterized by GT1a R155K (38/51) and GT1b D168 (26/46) substitutions. In the ICVR and relapse groups, 25.8% (25/97) had viruses lacking known resistant mutations.

Interpretation, Conclusion or Significance: The predominant NS3 resistant variants emerging from the 240 mg QD faldaprevir + PR groups were R155K (GT1a) or D168V (GT1b). 25.8% of post-treatment

rebound was wild-type without detectable resistant mutants. 240 mg QD faldaprevir + PR is being explored in phase III trials.

1710465

The Influence of a Low-fat Diet and Hospitalisation on Liver Function Tests in Healthy Japanese and Caucasian Male Volunteers Resident in a Phase I Unit for Up to 34 Days

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Statement of Purpose, Innovation or Hypothesis: There is a paucity of data on effects on liver function tests as a result of changes in diet and or hospitalisation of healthy subjects in Phase I clinical trials. Purkins et al. concluded that rises in transaminases and triglycerides in their study were caused by the carbohydrate content of the diet rather than its calorific value. Sucrose rather than starch was the carbohydrate which caused the rise in transaminases and triglycerides [1]. [1] Purkins et al. The influence of diet upon liver function tests and serum lipids in healthy male volunteers resident in a Phase I unit; Br J Clin Pharmacol. 2004 February; 57(2): 199–208

Description of Methods and Materials: To further investigate this, we have analysed the baseline and placebo data of 72 subjects with high LDL levels who were otherwise healthy and who were enrolled in a Phase I bridging study to investigate the LDL lowering properties of a newly licenced medicine. Subjects were resident for 34 days receiving a strict low fat diet consisting of 72% carbohydrates. All 72 subjects participated in a one week in house diet run in. Of those 16 volunteers (8 Japanese and 8 Caucasian) received placebo throughout the study; they were included into a sub group.

Data and Results: The data is presented using descriptive statistics. Alanine aminotransferase (ALT) was chosen as the main outcome parameter. We compared screening to on treatment values demonstrating no effect of diet and hospitalisation on ALT.

Interpretation, Conclusion or Significance: We conclude that a carbohydrate rich normo caloric diet in combination with hospitalisation for one week in 72 subjects and up to 34 days in a subgroup of 16 subjects did not affect ALT.

1690802

Investigation of Potential Pharmacodynamic and Pharmacokinetic Interactions Between Selexipag and Warfarin in Healthy Male Subjects

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Statement of Purpose, Innovation or Hypothesis: Patients with pulmonary arterial hypertension (PAH) have a deficiency in prostacyclin and prostacyclin synthase. Thus, targeting the prostacyclin pathway is an effective treatment option for PAH. Selexipag is a novel, orally available, selective prostacyclin receptor (IP) agonist, under development for the treatment of PAH. ACT-333679, the active metabolite of selexipag, is also a selective and potent agonist at the IP receptor.

Description of Methods and Materials: In this two-period crossover Phase 1 study, the potential pharmacodynamic and pharmacokinetic interactions between selexipag and warfarin were investigated in 18 healthy male subjects, 21–42 years of age. In Period 1, subjects received a single dose of selexipag or placebo on Day 1 followed by twice daily dosing on Days 2 to 12. In Period 2 subjects received the alternative, placebo or selexipag, treatment to that received in Period 1. Subjects received a single oral dose of 20 mg warfarin in the morning of Day 8 of both Periods.

Data and Results: Repeated administration of 400 μg selexipag had no influence on the rate and extent of absorption (AUC and C_{max}) of R- and S-warfarin. Selexipag $AUC_{0-\tau}$, ACT-333679 $AUC_{0-\tau}$, and ACT-333679 C_{max} at steady state were not affected by warfarin. Selexipag C_{max} was decreased by approximately 6% (not clinically significant). Steady-state levels of selexipag and ACT-333679 at a dose regimen of 400 μg b.i.d. selexipag had no influence on the pharmacodynamic variables INR $AUC_{(0\text{-}144h)}$, INR_{max}, or INR_{tmax}. Multiple doses of selexipag (400 μg) were well tolerated by subjects. There were no consistent differences in the number of treatment-emergent adverse events between subjects treated with selexipag and warfarin, and those treated with placebo and warfarin. There was no evidence of a drug effect on laboratory safety parameters, ECG, telemetry or orthostatic hypotension.

Interpretation, Conclusion or Significance: To conclude, there was no significant interaction between selexipag (400 μg multiple doses), ACT-333679 and warfarin (20 mg single dose).

[Correction added on October 14, 2013, after first online publication: In the original publication the order of the author's names was incorrect. The correct order is Séverine Niglis, Shirin Bruderer, Kaori Okubo, Hideya Mukai, Tim Mant, Jasper Dingemanse]

1693510

Pharmacokinetics of Fasiglifam (TAK-875), Simvastatin and Pravastatin Following Co-administration in Healthy Subjects

Ronald Lee[1], Sai Nudurupati[1], John Marcinak[1], Liping Pan[1], Miyako Sudo[2], Junzo Takahashi[2], Larry Kosobud[1], Xuejun Peng[1]

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Statement of Purpose, Innovation or Hypothesis: Fasiglifam (TAK-875) is a potent and highly selective agonist of G protein-coupled receptor 40 being developed as an adjunct to diet and exercise in patients with type 2 diabetes mellitus. Dyslipidemia is a common co-morbidity of diabetes, and as a result, it is possible fasiglifam may be co-administered with statins. This study evaluates the pharmacokinetics (PK) fasiglifam, simvastatin and pravastatin following coadministration in healthy subjects.

Description of Methods and Materials: Forty-two healthy male and female subjects were enrolled and administered the study drugs, and plasma PK determined. PK was assessed by point estimates and 90% confidence intervals (CIs) for the ratios (simvastatin + fasiglifam or pravastatin + fasiglifam to simvastatin, pravastatin or fasiglifam alone)

1693510: Study Design

Day	1	3	5-17	18	19	21
Dose	40 mg simvastatin	40 mg pravastatin	50 mg fasiglifam daily	50 mg fasiglifam	40 mg simvastatin + 50 mg fasiglifam	40 mg pravastatin + 50 mg fasiglifam
24-hour PK	simvastatin + simvastatin acid	pravastatin		fasiglifam + fasiglifam M-I	simvastatin + simvastatin acid + fasiglifam + fasiglifam M-I	pravastatin + fasiglifam + fasiglifam M-I

of the central values for simvastatin, simvastatin acid, pravastatin, fasiglifam and fasiglifam M I C_{max} and AUCs. A conclusion of no-effect was made if the 90% CIs were between 0.80–1.25. Safety was monitored throughout the study.

Data and Results: Assessing the effects of fasiglifam on simvastatin PK, the 90% CI for the ratio of the central values of simvastatin C_{max} was within the no effect range of 0.80–1.25; coadministration resulted in a 25% decrease in simvastatin AUCs and a 25–33% increase in simvastatin acid C_{max} and AUCs compared with simvastatin alone, and the 90% CIs were outside the no-effect range of 0.8–1.25. Assessing the effects of fasiglifam on pravastatin PK, and effects of either simvastatin or pravastatin on fasiglifam PK, the 90% CIs for pravastatin, fasiglifam and fasiglifam M-I C_{max} and AUCs were within the no-effect range of 0.80–1.25. All treatments were well tolerated.

Interpretation, Conclusion or Significance: Coadministration of fasiglifam with simvastatin or pravastatin had little to no effect on simvastatin, pravastatin or fasiglifam PK to be clinically meaningful.

1696735

Effects of Multiple-dose Fasiglifam (TAK-875) on the Pharmacokinetics and Pharmacodynamics of a Combination Oral Contraceptive: Ethinyl Estradiol and Levonorgestrel

Minh Vo, Ronald Lee, Ruishan Wu, John Marcinak, Larry Kosobud, Prabhakar Viswanathan

Takeda Global Research and Development Center, Inc., Deerfield, IL, USA

Statement of Purpose, Innovation or Hypothesis: Fasiglifam is a potent and highly selective agonist of GPR40 being developed as an adjunct to diet and exercise to improve glycemic control in patients with type 2 diabetes mellitus. Fasiglifam and a combination oral contraceptive (COC) will likely be administered together in females. This study evaluated the effects of fasiglifam on the pharmacokinetics and pharmacodynamics of ethinyl estradiol and norgestrel in healthy females.

Description of Methods and Materials: Thirty-one females aged 18 to 45 years completed the study. Subjects received ethinyl estradiol 30 μg/levonorgestrel 150 μg QD for two cycles (21 days active/7 days placebo per cycle) in a Lead-in Stabilization Period prior to Period 1. Subjects received one cycle of COC in Period 1, followed by 21 days of active COC with fasiglifam 50 mg in Period 2. Serial blood samples were collected on Days 21 of Periods 1 and 2 for quantitation of ethinyl estradiol and norgestrel. Sparse blood samples were collected for measurement of pharmacodynamic hormones (estradiol, progesterone, LH, FSH, SHBG) at baseline and Days 22 of each period. A conclusion of no effect of fasiglifam on the pharmacokinetics of ethinyl estradiol or norgestrel was reached if the 90% CIs for the ratio of C_{max} and AUC_{24} central values were within the 0.8 to 1.25 no-effect range.

Data and Results: The 90% CIs for the ratios of the C_{max} and AUC_{24} of ethinyl estradiol and norgestrel following administration of COC and COC + fasiglifam were within the range of 0.80–1.25. The mean observed values for pharmacodynamic hormones were similar between treatments.

Interpretation, Conclusion or Significance: Concurrent administration of fasiglifam 50 mg and ethinyl estradiol 30 μg/levonorgestrel 150 μg QD for 21 days had no effect on exposure to ethinyl estradiol and norgestrel and was well tolerated.

1699160

Evaluation of the Potential Drug Interaction of Fasiglifam (TAK-875) With Alogliptin or Metformin in Healthy Subjects

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Takeda Global Research and Development Center, Inc., Deerfield, IL, USA

Statement of Purpose, Innovation or Hypothesis: Fasiglifam (TAK-875), a potent, selective agonist of G-protein-coupled-receptor-40 which potentiates glucose-stimulated insulin secretion, is being developed as an adjunct to diet and exercise in patients with type-2 diabetes mellitus. Phase 1 studies were designed to evaluate the pharmacokinetics of fasiglifam, alogliptin and metformin after co-administration in healthy subjects.

Description of Methods and Materials: Subjects received a single dose of either alogliptin 25 mg (n = 26) or metformin 1000 mg (n = 27) on Day 1. Subsequently, fasiglifam 50 mg QD was administered for approximately two weeks to achieve steady state. Metformin or alogliptin was given with fasiglifam on Days 18 and 19, respectively. PK samples for alogliptin or metformin were collected for at least 72 hours after alogliptin or metformin dosing, and for fasiglifam/fasiglifam M-I for 24 hours on Days 17–18 and 18–19, respectively. PK parameters were estimated using non-compartmental methods. PK interactions were assessed by point estimates and 90% confidence intervals (CIs) of the ratios of the central values for C_{max} and AUC values using paired t-test.

Data and Results: Metformin was rapidly absorbed ($T_{max} \sim 1$ hr) and eliminated ($T_{1/2} \sim 14$ hr) following dosing of metformin alone or with fasiglifam; variability in metformin C_{max} and AUC values ranged from 19%-30%. Alogliptin was rapidly absorbed ($T_{max} \sim 2$ hr) and eliminated ($T_{1/2} \sim 21$ hr) following dosing of alogliptin alone or with fasiglifam; variability in alogliptin C_{max} and AUC values ranged from 10%–28%. Fasiglifam was absorbed ($T_{max} \sim 2$–3 hr) following dosing of fasiglifam alone or with alogliptin or with metformin; variability in fasiglifam C_{max} and AUC values ranged from 28%–50% whereas variability in fasiglifam M-I C_{max} and AUC values ranged from 57%–69%. The 90% CIs for C_{max} and AUC of metformin, alogliptin, fasiglifam/fasiglifam M-I when fasiglifam and metformin or fasiglifam and alogliptin were co-administered compared to those administered alone fell within the no-effect range of 0.80 to 1.25.

Interpretation, Conclusion or Significance: Co-administration of fasiglifam with metformin or alogliptin was well-tolerated with no hypoglycemia and no effects on PK of alogliptin, metformin, or fasiglifam/fasiglifam M-I.

1696735: Table

	Ethinyl Estradiol				Norgestrel			
	Mean COC	Mean COC + Fasiglifam	Point Estimate	90%CI	Mean COC	Mean COC + Fasiglifam	Point Estimate	90%CI
C_{max} (pg/mL)	93.9	91.0	0.98	0.93–1.03	6070	6130	1.02	0.97–1.07
AUC_{24}(pg.hr/mL)	809	775	0.95	0.92–0.97	77400	74400	0.97	0.92–1.02

1699359

Open Label Study to Evaluate the Pharmacokinetics of Retosiban (GSK221149) and Its Major Metabolite Co-administered With a High-fat Meal or Ketoconazole in Healthy Women of Child Bearing Potential

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Statement of Purpose, Innovation or Hypothesis: Retosiban is an oxytocin receptor antagonist, under development for the treatment of preterm labor. Part A of this study was to define the exposure of retosiban and its major inactive metabolite (GSK2847065) with/without a strong CYP3A4 inhibitor (ketoconazole). Part B was designed to determine the effect of food on the current retosiban tablet.

Description of Methods and Materials: This was a two-part randomized open label study. In Part A volunteers (n = 17) were administered retosiban 750 mg QD dose for three days. PK sampling took place on Days 1 and 3. On Days 5–9 subjects were administered ketoconazole 400 mg QD. On Day 10 ketoconazole plus 100 mg retosiban were coadministered and PK samples were taken over 24 hrs. Part B was a two-sequence, single dose randomized cross-over study (n = 29) designed to determine the PK of 750 mg retosiban under fasted and fed conditions.

Data and Results: Following oral administration of a single or repeat dose of 750 mg retosiban, the exposures of both parent and metabolite were similar. Mean Cmax and AUC metabolite to parent ratios ranged from 0.90 to 1.21 following 750 mg retosiban alone on Days 1 and 3. Mean dose normalized retosiban Cmax and AUC values significantly increased (5 to 8-fold), while mean dose normalized GSK2847065 Cmax and AUC values significantly decreased (36% to 80%) when 100 mg retosiban was co-administered with ketoconazole. Administration with food showed no clinically significant effect.

Interpretation, Conclusion or Significance: Mean peak and total exposures of retosiban and its metabolite were similar after single or repeat dose, suggesting that neither parent nor metabolite accumulates. Administration with ketoconazole resulted in a 5-8 fold increase in retosiban exposure, while metabolite exposures were decreased by 36–80% indicating that retosiban is highly metabolized by CYP3A4. No clinically significant food effect was observed. Retosiban may be administered without regard to meals. Parent and metabolite exposures were approximately equal. Retosiban was well tolerated when administered as a single 750 mg dose or in combination with 400 mg ketoconazole.

1704738

Pharmacokinetic and Pharmacodynamic Drug-Drug Interaction Assessment Between Pradigastat and Digoxin or Warfarin

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Statement of Purpose, Innovation or Hypothesis: Pradigastat (LCQ908), a novel diacylglycerol acyltransferase-1 inhibitor, was evaluated for potential pharmacokinetic (PK) drug-drug interaction (DDI) when co-administered with digoxin or warfarin in healthy subjects. The study also assessed potential pharmacodynamic (PD) DDI effects of pradigastat on warfarin as well as safety in the respective treatment arms.

Description of Methods and Materials: This open-label study included 2 parallel subject cohorts and 3 sequential treatment periods (Period 1 = digoxin (0.25 mg × 7 days) or warfarin (25 mg × 1 day), Period 2 = pradigastat (100 mg × 3 days, 40 mg × 7 days), Period 3 = combination of pradigastat + digoxin x 7 days or + warfarin x 1 day). Forty (40) subjects were enrolled in the study with 20 subjects allocated to each cohort. PK and PD (PT/INR for warfarin only) samples were collected in each period.

Data and Results: The statistical analysis results showed that the 90% CIs of the geometric mean ratios of digoxin, R-warfarin, and S-warfarin PK parameters (AUC and Cmax) were all within 0.80 to 1.25 interval. The 90% CIs of the geometric mean ratios of pradigastat PK parameters (AUC and Cmax) were within 0.80 to 1.25 interval when co-administered with warfarin; while co-administration with digoxin slightly reduced pradigastat exposure (~15%). The results also showed that 90% CIs of the geometric mean ratios of warfarin PD parameters (AUC PT, PTmax, AUC INR and INRmax) were within 0.80 to 1.25 interval. There were no SAEs or deaths in the study. All AEs were mild or moderate in severity.

Interpretation, Conclusion or Significance: Pradigastat had no clinical PK DDI effects on digoxin or warfarin and no clinical PD DDI effects on warfarin. Conversely, warfarin had no clinical PK DDI effects on pradigastat. Digoxin slightly reduced pradigastat exposure by ~15%, which is unlikely to be clinically significant. All treatments were well tolerated.

1705591

Assessment of Pharmacokinetic Interaction Between Pradigastat and Rosuvastatin in Healthy Volunteers

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Statement of Purpose, Innovation or Hypothesis: Pradigastat (LCQ908), a novel diacylglycerol acyltransferase-1 inhibitor, is under development for the treatment of patients with familial chylomicronemia syndrome. *In vitro*, it has been shown to inhibit the breast cancer resistance protein (BCRP), organic anion transporter polypeptide (OATP) -1B1, -1B3 and -2B1 transporters. This study was conducted to assess the potential for a drug-drug interaction between pradigastat and rosuvastatin, a substrate of BCRP and OATP transporters.

Description of Methods and Materials: In this open-label, single sequence study in thirty-six healthy subjects, rosuvastatin was dosed once daily at 10 mg for 7 days, followed by a 7 day washout period, and then pradigastat was dosed once daily at 100 mg loading dose for 3 days and 40 mg daily for 21 days. On Day 21, pradigastat 40 mg and rosuvastatin 10 mg were co-administered once daily for the next 7 days. Blood samples were taken to assess pharmacokinetics of both drugs as appropriate.

Data and Results: Under steady-state conditions of pradigastat, AUCtau,ss of rosuvastatin was unchanged (90% CI = 0.88, 1.01) while Cmax,ss decreased by 14% (90% CI = 0.79, 0.93). For pradigastat, the

AUCtau,ss (90% CI = 0.98, 1.11) and Cmax,ss (90% CI = 0.91, 1.06) remained unchanged. Co-administration of rosuvastatin and pradigastat was safe and well tolerated in healthy volunteers in this study.

Interpretation, Conclusion or Significance: The AUCtau,ss and Cmax,ss of pradigastat were not affected when it was co-administered with rosuvastatin. The AUCtau,ss of rosuvastatin was similar when dosed alone or with pradigastat under steady-state conditions, while its Cmax,ss was decreased by 14% which is not considered clinically relevant. These data suggest that pradigastat is unlikely to be an inhibitor of BCRP and OATP transporters *in vivo*.

1708165

The Pharmacokinetic (PK) Interaction Between Ranolazine (Ranexa®, ER) and Atorvastatin in Healthy Adult Volunteers in a Phase 1, Multiple-dose, Open-label, Fixed-sequence Study

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Statement of Purpose, Innovation or Hypothesis: Ranolazine is approved in US as a first line treatment for chronic angina at doses up to 1000 mg twice daily. In patients taking ranolazine for chronic angina, atorvastatin is co-administered for the management of dyslipidymia. Due to a shared CYP3A4 mediated metabolism, ranolazine and statins may interact. Levels of simvastatin, a sensitive CYP3A4 substrate, are increased 2-fold and the dose is restricted to 20 mg when co-administered with ranolazine. This study investigated the effect of ranolazine co-administration on the PK of atorvastatin, a frequently co-administered CYP3A4 substrate statin.

Description of Methods and Materials: Subjects received 80 mg atorvastatin qd from days 1–10, and 1000 mg ranolazine bid from days 6–10. Trough samples were collected pre-dose on all days and full PK plasma samples were collected at steady-state on day 5 (atorvastatin) and on day 10 (atorvastatin and ranolazine). PK parameters were calculated (NCA, Phoenix WinNonlin v6.2.1). Safety and tolerability were assessed.

Data and Results: Twenty three subjects completed the study. Steady state of atorvastatin and ranolazine were achieved. The geometric mean (95%CI) AUC0-τ for atorvastatin was 135.5 h × ng/mL (113.7, 161.4) when administered alone and 177.2 h × ng/mL (153.5, 204.6) when administered with ranolazine; corresponding values for Cmax were 35.8 ng/mL (29.1, 44.1) and 50.5 ng/mL (41.7, 61.1), respectively. A comparison of geometric means on the PK parameters showed that the AUC0-τ and Cmax for atorvastatin increased by 1.3 fold and 1.4 fold, respectively, when co-administered with ranolazine. There were no serious adverse events (AEs), or drug-related AEs leading to discontinuation. The most common AEs were nausea, dizziness and headache.

Interpretation, Conclusion or Significance: When co-administering with ranolazine 1000 mg bid, simvastatin has a dose-restriction, but atorvastatin 80 mg qd is well tolerated and may not require a dose-adjustment. The modest increase in atorvastatin exposure, when co-administered with ranolazine, was within the range of inter-subject exposure variability and was not clinically meaningful.

1708381

Co-administration with Gemfibrozil, Rifampicin or Probenecid Has No Clinically Relevant Effects on the Pharmacokinetics of Empagliflozin in Healthy Volunteers

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Statement of Purpose, Innovation or Hypothesis: Two open-label cross-over studies investigated potential interactions between empagliflozin (OATP1B1/1B3 and OAT3 substrate) and gemfibrozil (OATP1B1/1B3 and OAT3 inhibitor), rifampicin (OATP1B1/1B3 inhibitor) or probenecid (OAT3 and UGT inhibitor) in healthy volunteers.

Description of Methods and Materials: In one study, 18 healthy volunteers received a single dose of empagliflozin 25 mg, and gemfibrozil 600 mg twice daily (bid) for 5 days with a single dose of empagliflozin 25 mg on the third day. In a separate study, 18 healthy volunteers received a single dose of empagliflozin 10 mg, a single dose of empagliflozin 10 mg with a single dose of rifampicin 600 mg, and probenecid 500 mg bid for 4 days with a single dose of empagliflozin 10 mg on the second day. There was a ≥7-day washout period between empagliflozin treatments.

Data and Results: Exposure of empagliflozin was increased by co-administration with gemfibrozil (area under the plasma concentration-time curve from time of dosing extrapolated to infinity [$AUC_{0-\infty}$]: geometric mean ratio [GMR] 158.50%; 90% CI: 151.77-165.53; maximum plasma concentration [C_{max}]: GMR 115.00%; 90% CI: 106.15-124.59), rifampicin ($AUC_{0-\infty}$: GMR 135.20%; 90% CI: 129.58-141.06; C_{max}: GMR 175.14%; 90% CI: 160.14-191.56) and probenecid ($AUC_{0-\infty}$: GMR 153.47%; 90% CI: 146.41-160.88; C_{max}: GMR 125.60%; 90% CI: 113.67-138.78), but increases in empagliflozin exposure were <2-fold. All treatments were well tolerated.

Interpretation, Conclusion or Significance: Changes in empagliflozin exposure following co-administration of empagliflozin with gemfibrozil, rifampicin or probenecid are not considered to be clinically meaningful. These results indicate that the inhibition of OATP1B1/1B3 and OAT3 did not have a clinically relevant effect on empagliflozin exposure. Therefore, no dose adjustments of empagliflozin are necessary when co-administered with gemfibrozil, rifampicin or probenecid.

1708639

Pharmacokinetic Interactions Between INXN-1001, an Activator Ligand to the Adenoviral Vector Ad-RTS-IL-12, and Midazolam or Erythromycin in Healthy Subjects

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Statement of Purpose, Innovation or Hypothesis: A major obstacle for the development of effective immunotherapy is the ability of tumors to escape the immune system coupled with toxicity associated with systemic administration of immune-modulators. To overcome these challenges we developed an adenoviral vector, Ad-RTS-IL-12, administered intratumorally under the control of the RheoSwitch Therapeutic System® (RTS®) platform. Expression of IL-12 is regulated by oral administration of an activator ligand, INXN-1001. *In vitro* studies suggest that INXN-1001 is both a substrate and an inhibitor of CYP3A4. Therefore INXN-1001 has the potential to be involved in drug-drug interactions with agents that effect, or are affected by, CYP3A4.

Description of Methods and Materials: An open label fixed-sequence crossover study in 16 healthy subjects was conducted to investigate possible interactions between INXN-1001 and erythromycin (a moderate CYP3A4 inhibitor) or midazolam (primarily metabolized by CYP3A4). Subjects were administered a single oral dose of 2 mg

midazolam on Day 1, followed by once-daily oral doses of 60 mg INXN-1001 on Days 2–5, and a single oral dose of 2 mg midazolam + 60 mg INXN-1001 on Day 6. After treatment-free washout on Days 7–13, subjects were administered twice-daily oral doses of 500 mg erythromycin + once-daily oral doses of 60 mg INXN-1001 on Days 14–18.

Data and Results: Compared to INXN-1001 administered alone, co-administration with erythromycin resulted in 56% and 47% increase in INXN-1001 C_{max} and AUC, respectively, coupled with increase in $t_{1/2}$ (from 13.9 ± 4.2 h to 19.9 ± 5.2 h) and decrease in clearance (from 45.0 ± 9.9 L/h to 30.9 ± 7.8 L/h). When co-administered with midazolam there was a 23% decrease in INXN-1001 C_{max} but no impact on AUC and clearance. INXN-1001 + midazolam resulted in 17% and 31% increase in midazolam C_{max} and AUC, respectively, but similar $t_{1/2}$.

Interpretation, Conclusion or Significance: Significant pharmacokinetic interactions between INXN-1001 and erythromycin or midazolam were observed. This should be considered when INXN-1001 is administered concomitantly with drugs that are known to inhibit or substrates for CYP3A4.

1708685

Effect of Co-administration of Qsymia (Phentermine and Topiramate Extended-release) With Metformin, Sitagliptin or Probenecid

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Statement of Purpose, Innovation or Hypothesis: Qsymia is a fixed-dose combination of phentermine hydrochloride and extended-release topiramate, approved for once-daily (QD) combination treatment for patients struggling with obesity. This study examined the effect of Qsymia co-administration with metformin or sitagliptin, drugs likely to be co-administered with Qsymia. Co-administration of probenecid was also examined, to test for renal tubular re-absorption.

Description of Methods and Materials: This was an open-label, non-randomized, fixed-sequence, single-center, crossover study. Twenty subjects were to receive metformin twice daily (BID) on Days 1 through 4, QD on Day 5, and BID on Days 30 through 34; sitagliptin QD on Days 6 through 10 and 35 through 39; Qsymia QD on Days 11 through 39; and a single dose of probenecid on Day 29. Serial blood samples were drawn for the determination of metformin (Days 5 and 34), sitagliptin (Days 10 and 39), and phentermine and topiramate (Days 28, 29, 34, and 39), using a validated LC-MS/MS method. Pharmacokinetic parameters were derived using noncompartmental analysis. Analysis of variance was performed on ln transformed Cmax and AUCinf using SAS® Proc Mixed. Nonparametric comparisons of tmax were conducted using Wilcoxon Signed Ranks Test.

Data and Results: The statistical comparisons of plasma phentermine and topiramate Cmax and AUCinf at steady-state suggested phentermine and topiramate exposures were unaffected by metformin, sitagliptin, or probenecid co-administrations (90% confidence intervals for each comparison were within 80 to 125%). The statistical comparisons of Cmax and AUCinf at steady-state suggested plasma sitagliptin exposure was unaffected by Qsymia co-administration. The statistical comparisons of plasma metformin pharmacokinetic parameters at steady-state demonstrated mean maximum (Cmax) and overall (AUCinf) metformin exposure increased by approximately 16% and 23%, respectively, following Qsymia co-administration. The nonparametric statistical comparisons of plasma phentermine, topiramate, sitagliptin, and metformin tmax values did not show any significant drug interaction effects.

Interpretation, Conclusion or Significance: No clinically significant drug interactions were observed between Qsymia and sitagliptan or metformin; no dose adjustment is recommended. Phentermine and topiramate exposures in Qsymia were unaffected by blocking renal tubular re-absorption.

1708709

Effect of Pradigastat, a DGAT1 Inhibitor, on Acetaminophen Pharmacokinetics in Healthy Volunteers

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Statement of Purpose, Innovation or Hypothesis: Pradigastat is a diacylglycerol acyltransferase-1 inhibitor being developed for the treatment of chylomicronemia. Pradigastat has been shown to delay meal time gastric emptying in preclinical models. Therefore, this study was conducted to evaluate the effect of pradigastat on the pharmacokinetics of acetaminophen, a drug whose absorption is associated with gastric emptying rate.

Description of Methods and Materials: In this cross over study, healthy subjects (N = 25) were randomized in a seven treatment period, five-sequence design. Aectaminophen 1000 mg was administered in Period 1 with meal (Reference). In Peroid 2, steady state pradigastat levels were achieved by administering pradigastat 100 mg loading dose (Days 1 to 3) and 40 mg maintenance dose (Days 4 to 10) one hour prior to meal, which were maintained through Periods 3 to 7. During Periods 3 to 7, acetaminophen was administered at −2, −1, 0, +1, and +3 hours with respect to the meal time, respectively. Serial blood samples were collected during Period 1 and Periods 3 through 7 to analyze acetaminophen concentrations using a validated LCMS/MS method. Trough samples were collected to measure steady state levels of pradigastat. The pharmacokinetic parameters of acetaminophen were measured and compared with the reference treatment.

Data and Results: Pradigastat did not significantly change the Cmax and AUCs of acetaminophen as the 90% confidence intervals were within the 80 – 125% range for all treatment conditions. Furthermore, pradigastat did not alter the Tmax of acetaminophen in all treatments except for one, wherein slight delay by 53 minutes was observed when acetaminophen was administered at 1 hour post meal ingestion. There were mild gastrointestinal adverse events without clinically significant abnormalities in safety labs or vital signs.

Interpretation, Conclusion or Significance: Steady state pradigastat does not alter the AUC or Cmax of acetaminophen when dosed with a meal, suggesting that pradigastat may not alter the pharmacokinetics of drugs whose absorption is dependent on the rate of gastric emptying.

1709642

Topical Diclofenac Does Not Affect the Antiplatelet Properties of Aspirin as Compared to the Intermediate Effects of Oral Diclofenac: A Prospective, Randomized, Complete Crossover Study

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Encore Presentation: *The abstract was never published. It was however, given as a poster presentation without publication of the abstract. Nezami BM, Westphal ES, Rainka MM, Rowcliffe MM, Bates V, Gengo FM. Topical diclofenac does not affect the antiplatelet properties of aspirin as compared to the intermediate effects of oral diclofenac: a prospective, randomized, complete crossover study. Poster session presented at: The Midyear 2012. 2012 American Society of Health-System Pharmacists Midyear Meeting & Exhibition; 2012 Dec 2–6; Las Vegas, NV.*

Statement of Purpose, Innovation or Hypothesis: The purpose of this study is to determine whether the topical non-steroidal anti-inflammatory drug (NSAID), diclofenac, interferes with the antiplatelet effects of aspirin (ASA) 325 mg as well as address discrepancies reported regarding the interaction between aspirin and oral diclofenac. Such an interaction could potentially put patients at increased risk for cardiovascular and stroke events.

Description of Methods and Materials: The institutional review board approved this study which included 12 healthy men and women ages 18–50 years. Participants with any systemic disease or use of medication known to affect platelet function or count, or use of ethanol, tobacco, or other NSAID use were excluded. Treatments consisted of ASA 325 mg, diclofenac potassium 50 mg, topical diclofenac epolamine 1.3% patch, diclofenac potassium 50 mg followed by ASA 325 mg 2 hours later, and topical diclofenac epolamine 1.3% patch followed by ASA 325 mg. Platelet responsiveness was determined using whole blood impedance aggregation to arachidonic acid (AA) 0.5 mM and collagen 1 μg/ml and 5 μg/ml. For the patch and patch plus ASA treatment arms blood was drawn until platelet function returned to baseline at 21, 23, 35, 37, 29, 33 hours after placement of the first patch and every 24 hours following that and for all other arms at 0, 2, 4, 6, 8, 12 and every 24 hours post dose.

Data and Results: There were no statistically significant differences in ohms of impedance at any time points between the diclofenac epolamine patch plus ASA versus ASA alone ($p > 0.05$). Divergences in the data showed that some participants demonstrated significant platelet inhibition in response to ASA in the presence of diclofenac potassium at hours 2, 4, 6, 8, 12 ($p = 0.0011$, 0.0006, 0.0002, 0.048) for AA and hours 2 and 8 ($p = 0.0049$, 0.002) for collagen, as compared to ASA alone. Other participants demonstrated partial to no platelet inhibition with significance at hour 2 ($p = 0.0001$) for AA and collagen ($p = 6E\text{-}05$).

Interpretation, Conclusion or Significance: Topical diclofenac does not significantly interfere with the antiplatelet effects of ASA 325 mg. It therefore may be a safer alternative to the oral formulation which showed a mixed effect and may consequently put some patients at increased risk for cardiovascular and stroke events.

1710099

Effect of Repeated Oral Doses of Teriflunomide on a Single Oral Dose of Caffeine, Omeprazole, and Metoprolol Administered as a Cocktail in Healthy Male Subjects

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Statement of Purpose, Innovation or Hypothesis: To assess the effect of repeated doses of teriflunomide on the pharmacokinetics (PK) of caffeine (and its metabolite), omeprazole, and metoprolol, used as known probe substrates for cytochrome P450 (CYP) 1A2, CYP2C19, and CYP2D6, respectively. Teriflunomide is a novel, once-daily, oral immunomodulator approved in the US, Australia and Argentina for patients with relapsing MS. *In vitro* studies indicated that teriflunomide may inhibit and/or induce the activity of CYP1A2, CYP2C19, and CYP2D6. Therefore, a study was undertaken in healthy volunteers to assess its interaction with substrates of these CYPs.

Description of Methods and Materials: This open-label, single-sequence, two-period crossover study was conducted in 36 healthy adult male subjects. Subjects received concomitant single oral doses of caffeine (100 mg), omeprazole (20 mg), and metoprolol (100 mg) on Day 1 of Period 1 and Day 12 of Period 2. Teriflunomide was administered during Period 2 as a loading dose (70 mg/day) for 4 days followed by a maintenance dose (14 mg/day) for 9 days. This dosing regimen was used to mimic steady-state concentrations, due to the long half-life of teriflunomide. Poor metabolizers for CYP2C19 and CYP2D6 were excluded. The effect of teriflunomide on the non-compartmental PK parameters of each cocktail probe was evaluated by calculating their geometric mean ratios (for teriflunomide + cocktail *vs* cocktail alone) with 90% confidence intervals. Adverse events (AEs) were recorded.

Data and Results: Repeated doses of teriflunomide decreased the geometric mean AUC of caffeine (CYP1A2 substrate) by 55%. Teriflunomide administration had no effect on the PK of omeprazole or metoprolol. No serious AEs were observed and no treatment discontinuations occurred due to AEs.

Interpretation, Conclusion or Significance: Teriflunomide is a weak inducer of CYP1A2, but is not an inhibitor and/or an inducer of CYP2C19 or CYP2D6. The treating physician should be aware that when teriflunomide patients are co-treated with CYP1A2 substrates (e.g. duloxetine, alosetron, theophylline, tizanidine), there is a potential for exposure to these compounds to be increased.

1710175

Evaluation of the Effect of Quinidine, a Strong Pgp Inhibitor, on the Pharmacokinetics and CNS Distribution of Naloxegol

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Statement of Purpose, Innovation or Hypothesis: Purpose: Naloxegol is a substrate of Pgp transporter. The purpose of this study was to investigate the effect of quinidine, a strong Pgp inhibitor, on its PK and CNS distribution. In addition, the effect of morphine administered at a dose known to reduce GI motility on the PK of naloxegol was also evaluated.

Description of Methods and Materials: Methods: This study was conducted as a double-blind, randomized, 2-part, crossover, single-center study. In Part 1, the effect of quinidine on the pharmacokinetics of naloxegol was evaluated. A total of 38 volunteers received Treatment A (a single oral dose of naloxegol 25 mg and quinidine placebo) or Treatment B (naloxegol 25 mg and quinidine 600 mg), separated by a 7-day washout period. In Part 2, the effect of quinidine on potential changes in the CNS distribution of naloxegol was evaluated using morphine induced miosis effect as a biomarker. A subset of volunteers from Part 1 ($N = 14$) received either Treatment C (oral administration of naloxegol 25 mg and quinidine placebo and intravenous administration of 5 mg/70 kg morphine) or Treatment D (oral administration of naloxegol 25 mg and quinidine 600 mg and intravenous administration of 5 mg/70 kg morphine), separated by a 7-day washout period treatment. The effect of morphine on the PK of naloxegol was evaluated by comparing the PK parameters of naloxegol in Treatment A and Treatment C.

Data and Results: Results: Co-administration of the Pgp inhibitor quinidine resulted in a 1.38-fold increase in the AUC and a 2.45-fold increase in the Cmax of naloxegol. Co-administration of naloxegol and quinidine did not antagonize the morphine-induced miosis effect, suggesting that Pgp inhibition does not meaningfully impact restriction of naloxegol from the CNS space at therapeutic doses. The PK of

naloxegol was not affected by morphine administered via intravenous administration at 5 mg/70 kg. No safety or tolerability concerns were identified in healthy volunteers who received 25 mg naloxegol alone or in combination with morphine and/or quinidine.

Interpretation, Conclusion or Significance: Conclusion: Co-administration with quinidine causes a modest effect on the AUC and moderate effect on the Cmax of naloxegol but no apparent relevant impact on its CNS distribution based on pupillary miosis assessment. The PK of naloxegol was not affected by an IV dose of morphine known to reduce GI motility.

1710215

Effect of Repeated Oral Doses of Teriflunomide on the Pharmacokinetic Profile of Repaglinide in Healthy Male Subjects

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Statement of Purpose, Innovation or Hypothesis: To assess the effect of repeated doses of teriflunomide on the pharmacokinetics (PK) of repaglinide, a probe substrate for cytochrome P450 (CYP) 2C8. Teriflunomide is a novel, once-daily, oral, immunomodulator approved in the USA, Australia and Argentina for relapsing forms of multiple sclerosis (RMS). *In vitro* studies indicated that teriflunomide may inhibit CYP2C8 activity. *In vivo*, teriflunomide is a weak CYP3A inhibitor and an OATP1B1 inhibitor. As repaglinide is mainly metabolized by CYP2C8, to a minor extent by CYP3A, and may be transported by the organic anion transporting protein OATP1B1, teriflunomide interaction with repaglinide was assessed.

Description of Methods and Materials: This open-label, single-center, two-period and two-treatment single sequence study was conducted in 20 healthy adult male subjects. Subjects received a low single oral dose of repaglinide (0.25 mg) on Day 1 (Period 1) and Day 12 (Period 2). Teriflunomide was administered during Period 2 as a loading dose (70 mg/day) for 4 days followed by a maintenance dose (14 mg/day) for 8 days. This dosing regimen was used to mimic steady-state concentrations, due to the long half-life of teriflunomide. The effect of teriflunomide on PK variables of repaglinide was evaluated by calculating their geometric mean ratios (teriflunomide + repaglinide *vs* repaglinide alone) with 90% confidence intervals. Adverse events were recorded.

Data and Results: Repeated doses of teriflunomide increased the repaglinide geometric mean C_{max}, AUC_{last} and AUC by 1.64- (1.44-1.87), 2.25- (2.01-2.52) and 2.28- (2.04-2.54) fold, respectively. No serious or severe AEs were reported during the study and teriflunomide was generally well tolerated when administered alone or with repaglinide.

Interpretation, Conclusion or Significance: The observed effects of teriflunomide on the PK of repaglinide may result from CYP2C8 inhibition combined with a minor inhibition of CYP3A and OATP1B1. Therefore, treating physicians should be aware that when teriflunomide patients are co-treated with CYP2C8 substrates such as repaglinide, paclitaxel, pioglitazone or rosiglitazone, there is a potential for exposure to these compounds to be decreased.

1710488

Design Features and Results of Drug-Drug Interaction Trials Between Oral Contraceptives and Antiviral Drugs

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Statement of Purpose, Innovation or Hypothesis: Construct a database of drug-drug interaction (DDI) trials that evaluate the effect of antiviral (AV) drugs on oral contraceptives (OC) to understand the major design features of these trials.

Description of Methods and Materials: Design features and results of OC-AV DDI trials were collected from drug labels and clinical pharmacology reviews available at drugs@fda. The database contains information regarding trial design (number of menstrual cycles evaluated, population, type of OC used) and results (pharmacokinetic parameters, pharmacodynamic markers, and clinical recommendations in AV drug labels).

Data and Results: Data were available from 19 drugs and 22 trials. Eight trials (36.4%) consisted of three menstrual cycles (28-days each), six trials (27.2%) consisted of two menstrual cycles, and eight trials (36.4%) were conducted within one menstrual cycle. Twenty one trials (95%) enrolled healthy women of which 9 trials enrolled women previously stable on OC. Only one trial enrolled HIV-infected women. Norethindrone (1 mg)/ethinyl estradiol (35 μg) was the most widely evaluated OC (n = 9/22, 41%) followed by norgestimate (0.18/0.215/0.25 mg)/ethinyl estradiol (35 μg) (n = 5/22, 23%). The remaining eight trials evaluated eight different OC. The design of eighteen trials (82%) included multiple dose administration of OC, whereas four trials included single dose administration of OC. Pharmacokinetics were evaluated in all trials and only eight trials (36.4%) assessed at least one pharmacodynamic marker. Thirteen AV drug labels provided clinical recommendations for co-administering OC with AVs. Of these 13 labels, eight recommend using additional or alternative methods of birth control during AV treatment. Two labels allow co-administration of OC with AVs, and three labels include a contraindication of OC administration with AVs. The remaining 6 labels report the magnitude of drug interaction between OC and AVs, but do not include recommendations.

Interpretation, Conclusion or Significance: The database serves as a useful repository of information collected from DDI trials between OC and AV drugs. The information can address a variety of regulatory questions pertaining to trial design, conduct, and interpretation of trial results. The database can be used to identify the most informative OC-AV DDI trial design.

1717138

Regulation of Hepatic Cytochrome P450 Enzymes by 17-alpha Hydroxyprogesterone Caproate in Primary Cultures of Human Hepatocytes

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Statement of Purpose, Innovation or Hypothesis: 17-alpha hydroxyprogesterone caproate (17-OHPC) reduces the rate of preterm birth by 33%. 17-OHPC is known to be metabolized by CYP3A enzyme. Given that patients on 17-OHPC may be on other drugs that are also metabolized by CYP enzymes, it is important to understand the potential impact of 17-OHPC on the activity of various CYP enzymes in the liver.

Description of Methods and Materials: Primary human hepatocytes from two male donors were treated with vehicle or 17-OHPC for 72 hours, followed by 1-hour incubation of a validated CYP cocktail of phenacetin (CYP1A2), testosterone (CYP3A4/5), diclofenac (CYP2C9), S-mephenytoin (CYP2C19) and dextromethorphan (CYP2D6). The activities of major human cytochrome P450 enzymes in primary human hepatocytes was assayed by quantitating the metabolites derived from each of the above substrates using liquid chromatography-tandem mass spectrometry (LC-MS/MS). The expression of the major CYPs mRNA was also examined by qRT-PCR.

Data and Results: The results showed that 17-OHPC at 1 μM moderately increased the activity of CYP1A2 (1.3-fold), CYP2C19 (2.6-fold) and CYP3A4 (1.3-fold). 17-OHPC at 1 μM increased the mRNA expression of CYP1A2 (1.6-fold), CYP2C19 (1.9-fold), and CYP3A4 (2.2-fold). The induction of the activity of these enzymes by 17-OHPC was observed at a concentration of 0.1 μM and was concentration dependent. 17-OHPC did not significantly alter the enzyme activities or mRNA expression of CYP2C9 or CYP2D6.

Interpretation, Conclusion or Significance: Our results suggest that 17-OHPC may selectively alter the expression and activity of certain CYP enzymes and may moderately alter the pharmacokinetics of certain co-administered drugs.

1708258

Centhaquin Antinociception in Mice is Mediated by α_{2A} and α_{2B} But Not α_{2C} Adrenergic Receptors

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Statement of Purpose, Innovation or Hypothesis: The use of clonidine as a primary and adjuvant analgesic is well-documented. It is known that imidazoline and α_2-adrenergic receptors are involved in clonidine antinociception. Clonidine also produces antihypertensive actions mediated through the central nervous system. We have reported that centhaquin, a centrally acting anti-hypertensive drug, produces its hypotensive effect through a mechanism similar to that of clonidine. Centhaquin has also been shown to possess significant antinociceptive activity which is partially blocked by yohimbine, idazoxan, and naloxone. However, the involvement of specific adrenergic receptor subtypes (α_{2A}, α_{2B}, or α_{2C}) in centhaquin antinociception is unknown. The present study was conducted to determine antinociceptive properties of centhaquin citrate, a water soluble salt of centhaquin, and involvement of α_{2A}-, α_{2B}-, or α_{2C}-adrenergic receptors in mice.

Description of Methods and Materials: BRL-44408 (α_{2A}-adrenergic receptor antagonist), imiloxan (α_{2B}-adrenergic receptor antagonist) and JP-1302 (α_{2C}-adrenergic receptor antagonist) were used to determine the involvement of α_{2A}-, α_{2B}-, or α_{2C}-adrenergic receptors, respectively. Antinociceptive responses were determined by the tail-flick and hot-plate latency methods in male Swiss-Webster mice treated with centhaquin citrate alone and in combination with BRL-44408, imiloxan, or JP-1302. Parameters were measured for 360 min and expressed as Mean ± S.E.M. N = 8 per group.

Data and Results: Centhaquin citrate produced significant antinociceptive responses in mice ($P < 0.05$) which were blocked by BRL-44408 (tail-flick test: 49.75% decrease, $P < 0.05$; hot-plate test: 49.12% decrease, $P < 0.05$) and imiloxan (tail-flick test: 46.98% decrease, $P < 0.05$; hot-plate test: 46.42% decrease, $P < 0.05$). Centhaquin citrate antinociception was not affected by JP-1302 in both tail-flick and hot-plate latency tests over the 6-hour observation period.

Interpretation, Conclusion or Significance: This is the first report demonstrating centhaquin citrate antinociception and its blockade by BRL-44408 and imiloxan. We conclude that α_{2A} and α_{2B} but not α_{2C} adrenergic receptors are involved in centhaquin antinociception in mice.

1708268

Alteration in the Brain ET_B Receptor Binding Characteristics Following Cerebral Ischemia

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Statement of Purpose, Innovation or Hypothesis: Stimulation of endothelin ET_B receptors by IRL-1620 has been shown to provide neuroprotective effect in middle cerebral artery occlusion (MCAO) model of cerebral ischemia in rats. However, it is not known whether characteristics of ET_B receptors in the brain are altered following cerebral ischemia. We have therefore conducted this study to determine changes in binding characteristics of ET_B receptors in the brain, 1 and 7 days following MCAO.

Description of Methods and Materials: MCAO was produced in male Sprague Dawley rats using a 4.0 monofilament guided through the right external carotid artery to the middle cerebral artery. Binding studies were performed using [^{125}I]-IRL-1620 (specific activity 2200 Ci/mmol) as the radioligand and cold IRL-1620 (0–32 nM) as displacer. Non-specific binding was determined using 1 μM concentration of IRL-1620. K_d and B_{max} values were calculated using GraphPad Prism version 5.00 for Windows (GraphPad Software, San Diego, CA, USA).

Data and Results: On day 1 and day 7, MCAO rats displayed marked neurological and motor function deficit as evidenced by a high foot fault error (60 ± 16% and 35 ± 7%, respectively; $P < 0.01$) and a reduced ability to remain on the rota rod ($P < 0.05$). No deficits were observed in sham-treated animals. The infarct volume of MCAO rats was 126 ± 40 mm3 and 153 ± 22 mm3 on day 1 and day 7, respectively. Binding characteristics (K_d and B_{max}) were not altered at 24 hours post MCAO. However, a significant decrease in K_d values of ET_B receptor binding in both left and right hemispheres was observed 7 days post-MCAO. The decrease in K_d in the right (ischemic) hemisphere was significantly ($P < 0.001$) greater compared to left (non-ischemic) hemisphere. B_{max} was increased in both left and right hemispheres with the right hemisphere showing a significantly ($P < 0.001$) greater increase compared to the left hemisphere.

Interpretation, Conclusion or Significance: An increase in the density and affinity of ET_B receptors on the 7th day of cerebral ischemia could be an attempt to provide neuroprotection of ischemic brain.

1708383

New Phthalimide Derivatives as Potent Anti-obesity and Lipid-lowering Agents

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Statement of Purpose, Innovation or Hypothesis: Obesity is a serious condition associated with accumulation of fat inside body that also predisposes the subject to other complicated disorders. Inhibition of pancreatic lipase enzyme that regulates absorption of lipids in gastrointestinal tract is an effective strategy to counter obesity and high levels of lipids in blood. Orlistat acts via this mechanism and hence was selected as the standard drug in this study. Phthalimide moiety is capable of being employed to generate new anti-obesity drugs and thus three new derivatives were synthesized which also possess partial resemblance to the structure of orlistat.

Description of Methods and Materials: The animals were administered doses of test and standard drug of 100 mg/kg,p.o. and 250 mg/kg,p.o. respectively for 8 days and body weight of each animal of all groups was measured on ninth day of treatment to calculate loss of body weight. Triton was administred in 400 mg/kg, i.p. dose to induce hyperlipidaemia. Both serum cholesterol and triglycerides level were measured for test, standard, positive control and negative control group animals on ninth day of the treatment.

Data and Results: Each derivative produced significant reduction in bodyweight of animals when compared to negative control group animals. Triton produced elevation in serum cholesterol and triglycerides levels in the animals of positive control group at the dose of

1708383: Effect of test and standard drugs on bodyweight of animals

Sr No	Treatment	Weight(gm) DAY1	Weight(gm) DAY9	Loss of Weight (gm)
1	Negative control	300	295	5
2	Orlistat	325	245	80
3	ST7	325	257	68
4	ST8	310	236	74
5	ST5	305	200	105

400 mg/kg i.p. At the same time, orlistat and other synthesized derivatives prevented rise in serum cholesterol and triglycerides levels in animals of respective groups at the dose of 250 mg/kg and 100 mg/kg respectively when given orally.

Interpretation, Conclusion or Significance: It can be concluded that these new derivatives possess considerable action as anti-obesity and lipid lowering agents. Further experiments are undergoing to elucidate their exact mechanism in obesity and hyperlipidaemia.

1709271

Evaluation of the Effect of Mexiletine as a Promising New Drug for the Treatment of Progressive Alzheimer's Disease Using Various Experimental Animal Models

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Encore Presentation: *Nandha K H, Amirthalingam S. Evaluation of the Effect of Mexiletine as a Promising New Drug for the Treatment of Progressive Alzheimer's Disease Using Various Experimental Animal Models. Inventi Rapid: Molecular Pharmacology, 2013(2):1–5, 2013.*

Statement of Purpose, Innovation or Hypothesis: Alzheimer's disease is one of the most serious neurodegenerative disorders occurring mainly in the old age. It results into memory and cognitive impairment leading to inability to perform routine tasks in day to day life and worsening of quality of life. Excitotoxic-neurodegeneration caused by over functioning of glutamatergic transmission is of the main pathophysiological aspects. Glutamate release is mainly mediated by sodium channels and blockade of these channels decreases the excessive release of this excitatory neurotransmitter.

Description of Methods and Materials: Aluminum chloride, a well known neurotoxic compound, was administered at 100 mg/kg intraperitoneally for 45 days to induce Excitotoxic-neurodegeneration followed by memory impairment similar to Alzheimer's disease. Mexiletine was administered in high and low doses of 85 mg/kg and 60 mg/kg both intraperitoneally in their respective groups continuously throughout the induction period. Memantine was selected as a standard drug and was administered similarly. Cognitive functions were checked by Step-down latency model and elevated plus maze model.

Data and Results: Prolongation in step-down latency and shortening of transfer latency were observed in test and standard group animals indicating memory retention and the significant prevention of Alzheimer's disease in treated animals.

Interpretation, Conclusion or Significance: Mexiletine is effective at preventing ongoing memory impairment in Alzheimer's disease possibly by controlling excessive glutamate release through blockade of sodium channels.

1709288

Immunomodulation of CD4 Count by Phela, an Herbal Extract

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Statement of Purpose, Innovation or Hypothesis: Phela is an extract from a herbal medicine that is under development for use as an immune booster in immune compromised individuals. Unfortunately, the current dose for Phela was not evaluated scientifically. Therefore, the aim of this study was to determine the appropriate dose of Phela for immunomodulation.

Description of Methods and Materials: Four groups of 15 Sprague-Dawley rats each were treated daily with either normal-saline, Phela 5, 15.4 or 75 mg/kg, and in each group 5 rats were sacrificed after 7, 14 and 21 days of treatment. Blood was analysed for liver, renal and haematology functions, and the CD4 and CD8 cell counts were analysed by flow cytometry. The kidney, liver, spleen and thymus were weighed and examined for any pathology.

Data and Results: All the three doses of Phela led to increased white blood cell count after 14 days of treatment, and this was significant for

1709271: Effect of test and standard drug in SDL and TL of mice

Sr. No.	Treatment	SDL (training) in seconds	SDL (memory) in seconds
1	Negative control	7.6	>300
2	Positive Control (AlCl3 100 mg/kg)	6	11
3	Standard (Memantine HCl 20 mg/kg)	10	269
4	Test 1 (Mexiletine HCl 60 mg/kg)	8	221
5	Test 2 (Mexiletine HCl 80 mg/kg)	10	>300
Sr. No.	Treatment	TL (training) in seconds	TL (memory) in seconds
1	Negative control	55.6	24.9
2	Positive Control (AlCl3 100 mg/kg)	69.25	55.7
3	Standard (Memantine HCl 20 mg/kg)	72	38.7
4	Test 1 (Mexiletine HCl 60 mg/kg)	52	29.2
5	Test 2 (Mexiletine HCl 80 mg/kg)	45	21.5

Results are Expressed as Standard Arithmetic Mean of Each Group of Animals

doses 5 mg/kg (P = 0.02) and 15.4 mg/kg (P = 0.03). This was associated with increased lymphocyte count which correlated with increased CD4 count from day 7 to 14 of treatment. At 5 mg/kg, the CD4 count was 1.10 ± 0.15 at 7 days, and 2.48 ± 0.29 at 14 days (P = 0.005), while for 15 mg/kg, it increased from 1.30 ± 0.14 to 2.90 ± 0.19 (P = 0.001). The CD4 count in the control dropped progressively but remained in the normal range. Eosinophilia was also noted while CD8 count and physiological function tests were normal. This observation correlates with our previous report where Phela led to increased Interleukin-2.

Interpretation, Conclusion or Significance: In conclusion, Phela led to ample stimulation of the immune system as indicated by increased CD4 count at doses of 5 and 15 mg/kg. This selective effect implies that Phela can be indicated in diseases that interfere with CD4 count, but this needs to be confirmed in a diseased model

1709540

Exacerbation of Renal Injury Associated with Celecoxib by Concomitant Administration of Misoprostol in Rats: Effect of Misoprostol on Kidney Celecoxib Levels

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Statement of Purpose, Innovation or Hypothesis: Nonsteroidal anti-inflammatory drugs (NSAIDs) exert their side effects (e.g. gastrointestinal, renal) by reducing the production of prostaglandins (PGs). Misoprostol, a PG-based medicine, has been used for prevention of NSAID-induced gastric injury. In this study, we investigated the influence of concomitant administration of misoprostol with celecoxib (an NSAID) on the heart and kidney. We also compared kidney celecoxib levels in treated groups.

Description of Methods and Materials: Rats were randomly divided into 4 groups (n = 6). Two groups were administered, by oral gavage, placebo (methylcellulose 0.5%) and two groups received misoprostol (100 μg/kg) twice daily for 9 days. On days 3–9, one placebo and one misoprostol group received a single daily dose of celecoxib (40 mg/kg). On day 10, rats were euthanized and the heart and kidneys were collected. Tubular necrosis and dilatation and myocardium abnormalities were assessed by histological sectioning and staining (H&E) and graded on a scale of 0 to 3. Kruskal-Wallis one way analysis, followed by a post hoc test, was performed for histologic scores. An HPLC system was utilized to quantify kidney celecoxib levels and the data was analyzed using a Student's t-test and presented as mean ± standard error of the mean.

Data and Results: Groups receiving celecoxib or misoprostol plus celecoxib showed a significant increase in tubular necrosis compared to control. All groups receiving treatment showed significant increases in tubular dilatation. This was more severe in the group treated with misoprostol plus celecoxib (mean rank = 78.0, n = 4) compared to celecoxib group (mean-rank = 61.5, n = 6). In general, no significant histopathological changes were noted in the myocardium. However, one animal in celecoxib group and two animals in misoprostol plus celecoxib group exhibited a significant organizing pericarditis. Kidney celecoxib levels in celecoxib group (4.66 ± 1.47 μg/g, n = 6) were not significantly different (p = 0.92) from misoprostol plus celecoxib group (5.00 ± 3.18 μg/g, n = 5).

Interpretation, Conclusion or Significance: Our findings suggest that misoprostol exacerbates tubular dilatation when administered concomitantly with celecoxib without affecting kidney celecoxib levels.

1709617

The Development of a Whole Blood Impedance Aggregometry Assay to Differentiate Between Pharmacokinetic and Pharmacodynamic Aspirin Resistance Using Varying Concentrations of DMSO and Aspirin

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Encore Presentation: *The abstract was never published. It was however, given as a poster presentation without publication of the abstract. Snyder CE, Westphal ES, Rainka MM, Bates V, Gengo FM. The development of a whole blood impedance aggregometry assay to differentiate between pharmacokinetic and pharmacodynamic aspirin resistance using varying concentrations of DMSO and aspirin. Poster session presented at: The Midyear 2012. 2012 American Society of Health-System Pharmacists Midyear Meeting & Exhibition; 2012 Dec 2–6; Las Vegas, NV.*

Statement of Purpose, Innovation or Hypothesis: The purpose of this study is to determine the appropriate concentrations of dimethyl sulfoxide (DMSO) and aspirin (ASA) for use in an *ex vivo* blood test to classify ASA resistance as pharmacokinetic or pharmacodynamic in nature. This study will determine if DMSO significantly impacts platelet function when compared to ASA and an untreated control and if the addition of ASA to a blood sample *ex vivo* using DMSO as a solvent will significantly affect collagen and arachidonate induced platelet aggregation, as compared to an untreated control. An initial test classifying the physiology of a patient's resistance would allow them to be rapidly placed on an appropriately potent anti-platelet agent, and potentially prevent a secondary event from occurring.

Description of Methods and Materials: The institutional review board approved this prospective, unblinded, cross over study. Twelve healthy men and women, ages 18–50, were enrolled. Participants with history of bleeding or platelet function disorders, use of medications known to affect platelet function, or those who were found to be <80% compliant based on pill count, were excluded. Whole blood impedance aggregometry was used to assess each participant's platelet function while no platelet affecting drugs were being taken as well as after 7 to 10 days of 81 mg of ASA and 7 to 10 days of 325 mg of ASA. Dose order was based on a randomization scheme. Platelet function was assessed in each arm without any *ex vivo* additions (control) and following the addition of 1%, 0.5%, and 0.05% DMSO. Tests were also conducted with the in *ex vivo* addition of 100, 50, and 10 μmol/L of ASA dissolved in 1%, 0.5% or 0.05% DMSO, testing all combinations.

Data and Results: It was found that DMSO concentrations of 0.5% and 0.05% did not affect platelet aggregation to collagen 1 μg/ml (p = 0.2, p = 0.4) or to arachidonate 5 mM (p = 0.1, p = 0.2). The addition of ASA to a blood sample *ex vivo* in concentrations of 100, 50 and 10 μmol/L substantially affects platelet aggregation in these DMSO concentrations (p < 0.001).

Interpretation, Conclusion or Significance: The use of ASA concentrations 100, 50 and 10 μmol/L dissolved in DMSO concentrations of 0.5% and 0.05% show significant aggregation to collagen and arachidonate and therefore can be used in an assay to predict pharmacokinetic or pharmacodynamic ASA resistance.

1710261

Modeling the Ontogenesis of Hepatic Cytochrome P450s

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Statement of Purpose, Innovation or Hypothesis: The maturation of drug metabolizing enzymes is the predominant factor that accounts for age associated changes in pediatric pharmacokinetics. Each enzyme demonstrates an independent rate and pattern of development. In this study, the characteristic maturation patterns of the most important hepatic CYP enzymes including CYP1A2, 2C9, 2C19, 2D6, 2E1 and 3A4, were quantified as a continuous function of age from birth and the age of reaching the adult level.

Description of Methods and Materials: Individual CYP isozyme expression/activity data from hepatic microsomes in specific infant age groups were assembled from literature published from 1970–2012 in PubMed. The mean reported values stratified by age groups were compiled in the database. For each individual enzyme isoform, the mean values for each age group from different studies were pooled naively and fitted with several plausible non-linear regression functions using NONMEM version VI (Globomax LLC, Hanover, MD, USA). A proportional residual error model was used. Structural models were compared on the basis of the objective function value (OFV), visual inspection of fits, and the Akaike information criteria (AIC).

Data and Results: The development of CYP1A2, 2C9, 2C19, 2D6, 2E1 and 3A4 was best described by the hyperbolic function (Eq. 1) in the age range of observations. Table 1 lists the ontogeny parameter estimates for each enzyme isoform. $MF = MF0 + ((MFmax - MF0) \times AGE(day))/(TM50 + AGE(day))$ Equation 1

Interpretation, Conclusion or Significance: The high MF0 values for CYP2E1 suggested its fetal expression or prenatal onset, while the extremely low values of MF0 for CYP2C9 and 1A2 suggested the two isoenyzmes expression were triggered by birth effect. CYP2C9, 2C19 and 2D6 appeared to mature faster than CYP2E1, 3A4 and CYP1A2, as shown by the short half-life values within days compared to those in months. Because the maximal ratios of CYP1A2, 2C9, 2C19 and 2D6 are way below 1 due to insufficient data, the models could not describe the ontogeny profiles of these four enzymes beyond their observed age range.

1710261: Table 1 Maturation parameter estimates for individual cytochrome P450 (CYP) isoforms

Enzyme	Age range (day)	MF0	MFmax	TM50 (day)
CYP1A2	0.5–2273	0.0078	0.539	100
CYP2C9	0.5–1788	0	0.308	4.8
CYP2C19	0.5–1788	0.0856	0.538	6.1
CYP2D6	0.5–355	0.0128	0.461	15.1
CYP2E1	0.5–2273	0.216	0.869	183
CYP3A4	0.5–2273	0.0835	0.978	139

1710355

Endothelin B Receptor Agonist, IRL-1620, Prevents Aβ-induced Oxidative Stress and Cognitive Impairment in Normal and Diabetic Rats

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Statement of Purpose, Innovation or Hypothesis: Alzheimer's disease (AD) is a progressive brain disorder leading to impairment of learning and memory. Aβ-induced oxidative stress causes the initiation and progression of AD. Endothelin and its receptors have been considered as therapeutic targets in the treatment of AD. Recent studies indicate that stimulation of ETB receptors may provide neuroprotection. The purpose of this study was to determine the effect of selectively activating the ETB receptors following Aβ-induced cognitive impairment and oxidative stress in non-diabetic and diabetic rats.

Description of Methods and Materials: Adult male Sprague-Dawley rats were treated with Aβ1-40 (20 μg in 3 equally divided doses) in the lateral cerebral ventricles using sterotaxically implanted cannulas. Aβ was administered on day 1, 7 and 14 and all experiments were performed on day 15. The rats were treated chronically with ETB agonist (IRL-1620) and antagonist (BQ788) for 14 days. Oxidative stress markers assessed were malondialdehyde, glutathione and superoxide dismutase. Learning and memory behavior was assessed using the Morris water maze.

Data and Results: Aβ treatment in non-diabetic and diabetic rats produced a significant ($p < 0.0001$) increase in malondialdehyde (MDA) levels (516.13 ± 14.02 and 531.58 ± 10.21 nmol/g wet tissue, respectively) compared to sham group (112.1 ± 1.82 and 114.31 ± 2.05 nmol/g wet tissue, respectively). Antioxidants decreased following Aβ treatment compared to sham group. Treatment with IRL-1620 reversed these effects, indicating that ETB receptor activation reduces oxidative stress injury following Aβ treatment. Animals pretreated with BQ788 showed similar oxidative stress damage compared to vehicle group. In Morris swim task, Aβ treated rats showed a significant impairment in spatial memory. Rats treated with ETB receptor agonist, IRL-1620, significantly reduced the cognitive impairment induced by Aβ. However, Blockade of ETB receptors by BQ788 followed by either vehicle or IRL-1620 treatment resulted in cognitive impairment similar to those of rats treated with vehicle alone. BQ788 blocked IRL-1620 induced improvement in cognition and oxidative damage.

Interpretation, Conclusion or Significance: Results of the present study demonstrate that IRL-1620 administration prevents cognitive impairment and oxidative stress induced by Aβ suggesting that ETB receptor stimulation may be useful in neurodegenerative diseases. (Funding for this study was provided by Alzheimer's Drug Discovery Foundation - www.alzdiscovery.org).

1710526

Endothelin B Receptor Agonist, IRL-1620, Enhances Angiogenesis and Neurogenesis Following Cerebral Ischemia in Rats

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Statement of Purpose, Innovation or Hypothesis: Endothelin B (ETB) receptor agonist, IRL-1620, has been shown in previous studies, conducted in our lab, to provide significant neuroprotection at both 24 hours and 1 week following permanent cerebral ischemia. It is possible that IRL-1620 may be neuroprotective due to angiogenesis and neurogenesis. However, the effect of IRL-1620 on neurovascular remodeling following cerebral ischemia has not been established. The present study was conducted to determine the effect of IRL-1620 [Suc-[Glu9,Ala11,15]-Endothelin-1(8-12)] on astrocytes, neurons, and vascular endothelial cells after the induction of cerebral ischemia.

Description of Methods and Materials: Male Sprague-Dawley rats undergoing permanent middle cerebral artery occlusion (MCAO) received three intravenous injections of either vehicle or IRL-1620 (5 μg/kg) at 2, 4, and 6 hours post occlusion. Brain tissues of animals euthanized at 24 hours or 7 days post occlusion were processed

for immunofluorescent labeling of ETB receptors, astrocytes, neurons, and vascular and neuronal growth factors.

Data and Results: At 24 hours post occlusion, IRL-1620 treatment increased ETB receptor expression and preserved neuronal numbers in the cortex, striatum and subventricular zone (SVZ) of the ischemic rat brain. IRL-1620 also enhanced the number of blood vessels labeled with vascular endothelial growth factor (VEGF) when compared to vehicle treatment. By 1 week following MCAO, VEGF-positive vessels/30 μm brain slice in the IRL-1620 group numbered 11.33 ± 2.13 versus 4.19 ± 0.79 in the vehicle group ($P < 0.01$), indicating an increase in angiogenesis. Additionally, animals receiving IRL-1620 displayed an increased number of proliferating cells ($P < 0.0001$) and cells positively staining for nerve growth factor (NGFP < 0.0001) in the infarcted brain. NGF-positive cells in the cortex, striatum and SVZ of IRL-1620 treated animals numbered 2.29 ± 0.31, 2.08 ± 0.26, and 3.05 ± 0.38 per 100 μm2, respectively, demonstrating a significant increase in neurogenesis as compared to the vehicle group, which averaged less than 1 NGF-positive cell per 100 μm2. Pretreatment with ETB antagonist, BQ788, blocked the effects of IRL-1620 treatment, confirming the role of ETB receptors in the neurovascular remodeling actions of IRL-1620.

Interpretation, Conclusion or Significance: Results of the present study indicate that IRL-1620, administered on the day of infarct, is neuroprotective and enhances angiogenic and neurogenic remodeling following cerebral ischemia.

1710539

Effect of Centhaquin Resuscitation on Coagulation in a Rabbit Model of Uncontrolled Hemorrhagic Shock

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Statement of Purpose, Innovation or Hypothesis: It is known that aggressive resuscitation with crystalloids following hemorrhagic shock induces coagulopathy. Centhaquin is a cardiovascular active agent, which has been found to be effective in resuscitation of hemorrhagic shock. However, its effect on coagulation is not known. To determine the effect of resuscitation with centhaquin on blood coagulation in a rabbit model of uncontrolled hemorrhagic shock using thromboelastography (TEG).

Description of Methods and Materials: Male New Zealand white rabbits were anaesthetized and a laparotomy was performed and hemorrhage was induced by a single puncture to the abdominal aorta. Resuscitation with normal saline or centhaquin (0.05 mg/kg) was carried out after 15 minutes of aortic puncture to maintain the mean arterial pressure (MAP) at 45 mmHg for 60 minutes (hypotensive resuscitation). Each rabbit was then observed for an additional 60 minutes. In another group normal saline was infused at a higher rate to maintain MAP at 60 mmHg (normotensive resuscitation). The effect of centhaquin on arterial blood gases was determined using a blood gas analyzer, volume of infusion and blood loss were measured and coagulation was monitored by TEG.

Data and Results: Hypotensive resuscitation by saline required a volume of 207 ± 9 mL to maintain MAP at 45 mmHg which was significantly ($p = 0.001$) more than centhaquin (133 ± 11 mL). Volume (377 ± 11 mL) of saline needed for normotensive resuscitation (60 mm Hg) was markedly ($p < 0.0001$) greater compared to hypotensive resuscitation. Blood loss was similar in saline (40 ± 3 mL) and centhaquin (38 ± 2 mL) hypotensive resuscitation, however, it was significantly ($p < 0.05$) more with normotensive resuscitation. TEG parameters at baseline were $R = 11.4 \pm 0.6$ min, $K = 2.9 \pm 0.1$ min, $\alpha = 54.0 \pm 0.8^{\circ}$, $MA = 65.6 \pm 0.5$ mm. Hemorrhagic shock produced a decrease in R, K, MA and an increase in α. TEG did not differ significantly between groups at end of hemorrhage. Hypotensive resuscitation with saline produced no change in R, decreased K and MA, and increased α. Hypotensive resuscitation with centhaquin produced no change in R, K and α, compared to saline, however, MA increased significantly ($p < 0.02$). Normotensive resuscitation with vehicle produced no change in R, increased α ($p < 0.001$), decreased K ($p < 0.01$) and decreased MA ($p < 0.03$) compared to centhaquin.

Interpretation, Conclusion or Significance: TEG parameters are altered following resuscitation but less affected when hypotensive resuscitation is performed with centhaquin.

1717198

Stachytarpheta Indica (L.) Vahl: An Analysis for Novel Effects of Hepatic Drug Activities as Probes for Pharmacological Studies

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Statement of Purpose, Innovation or Hypothesis: Inhibited I phase of drug metabolism is a main reason for numerous side effects and increased drug toxicity, observed in the course of influenza virus infection. Stachytarpheta indica (L.) Vahl, a plant spread in Bangladesh, demonstrated significant antioxidant and antiviral activities. The studies are to evaluate the preventive effect of polyphenol complex from Stachytarpheta indica (L.) Vahl on the oxidative drug metabolism in influenza virus infection.

Description of Methods and Materials: The experimental model of influenza virus infection is developed in female wistar imprinting control region rats. Polyphenol complex is applied nasally (10 mg/kg). In liver, 9000 g supernatant thiobarbituric acid reactive substance (TBARS), and antioxidant total activity as well as monooxygenase N-demethylase activity (ethylmorphyne, amidopyrine, and analgin), and hydroxylase activity (aniline, and p-nitrophenol), NADPH-cytochrome P450 reductase, and cytochrome P450 content are determined. Student Fisher's t test and correlation coefficients are used for statistics.

Data and Results: High correlation between increased TBARS, and decreased monooxygenase activity ($p < 0.001$) is found in infected rats. It suggests that activation of free radicals can be one of the main reasons for unspecific monooxygenase inhibition, because all components of cytochrome P450 system are inhibited (mostly on the VIII and X days). Polyphenol complex pretreatment demonstrates significant preventive effect against increased levels of TBARS, and decreased antioxidant total activity. Drug metabolism in influenza virus infection rats is restored by polyphenol complex near to healthy controls.

Interpretation, Conclusion or Significance: TBARS probably play important role not only in the pathogenesis of influenza virus infection, but also in modulation of hepatic monooxygenase activity. All inhibited P450 monooxygenase activities are significantly restored by polyphenol complex pretreatment. The complex mechanism of polyphenol complex protective effect obviously combines several biological activities: antioxidant activity, selective antiviral, and protein-bounding effect. In contrast to infected rats, polyphenol complex has medium pro-oxidant and weak inhibiting effect on monooxygenases in healthy rats, probably related to its protein-binding effect on membrane proteins, and enzymes.

1710263

First-In-Human Clinical Program Design for New Entities: Comparison Between the Traditional Linear Approach and the Integrated Multiple Parts Approach

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Statement of Purpose, Innovation or Hypothesis: Comparison between 2 approaches to design first in human (FIH) clinical programs for assessment of safety and pharmacokinetics (PK) of new chemical entities: (1) Traditional linear approach of multiple studies, and (2) Integrated multiple parts approach.

Description of Methods and Materials: The present analysis is conducted over two Phase I FIH programs aiming (1) Safety and PK in Single Ascending Doses (SAD), (2) Safety and PK in Multiple Ascending Doses (MAD), and (3) Effect of food in a crossover design. Each of the SAD and MAD cohorts included 8 subjects (6 actives: 2 placebo); the food effect included 12 subjects. Program 1 followed the traditional linear approach where each of the 3 studies was designed in a separate protocol, using fixed dose levels established following completion of the previous study. Program 2 followed the integrated approach where multiple study parts were designed within one protocol prior to initiation of the clinical program. Additionally an adaptive approach was considered in this design to allow optional dose adjustment during the study conduct.

Data and Results: Both Programs were completed successfully. In FIH Program 1, 7-SAD cohorts and 6-MAD cohorts were completed together with the food effect study sequentially over a period of 15 months in total. In FIH Program 2, 5-SAD cohorts and 7-MAD cohorts were completed simultaneously together with the food effect study over a period of 6.5 months. Additionally, the adaptive approach offered flexibility to investigate new dose levels and adapt the dosing regimen for 2-MAD cohorts. Finally, the FIH Program 2 included a prescheduled Proof-of-concept patient arm that could be initiated following the MAD part and was completed within 2.5 months, for a total of 9 months for whole Program 2.

Interpretation, Conclusion or Significance: During early stage clinical development of new entities, the integrated multiple parts design approach primarily overcomes the long delay challenge experienced in the traditional linear approach, thus allowing an expedited entry into Phase II.

1710460

Quantitative Extrapolation of PK/PD Data from Adult Type 2 Diabetes Mellitus to Inform Pediatric Investigation Plans

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Statement of Purpose, Innovation or Hypothesis: The objective of this analysis is to develop an approach to extrapolation of PK/PD data for DPP4 inhibitors from adult T2DM patients to design an efficient and effective pediatric clinical investigation plan. Saxagliptin (SAXA) is used as a specific example.

Description of Methods and Materials: Recently published meta-analysis with DDP4 inhibitors was leveraged for integrating adult prior knowledge of the relationship between PK, PD (weighted average DPP4 inhibition) and hemoglobin A1c (HbA1c) response1. SAXA PK/PD relationship and inter-individual variability on treatment and placebo effect were estimated from an adult phase 3 trial (CV181011). To enable extrapolation to pediatric subjects (ages 10 to <18), the PK of SAXA was adjusted for changes in its elimination due to age and body size. Clinical trial simulations were performed to test alternative trial designs in pediatric patients, as well as alternative hypotheses of potency and efficacy in pediatric vs. adult patients. Demography (body weight, age and height) of T2DM pediatric subjects were sampled from NHANES database (1999–2010).

Data and Results: An alternative clinical trial design, powered to estimate dose-response (D-R) relationship for the change from baseline in HbA1c with high confidence (95% CI for estimate of placebo anchored D-R does not include zero) was evaluated. The subjects were randomized 1:1:1 for placebo, 2.5 mg/day SAXA, or 5 mg/day SAXA. Total sample size of 51 (efficacy/potency equivalent to adult) to 120 (low efficacy and potency) was predicted to provide ∼80% power. Similarly, total sample size of ∼90 subjects was predicted to provide power of ∼70% (low efficacy and potency) to 93% (efficacy/potency equivalent to adult).

Interpretation, Conclusion or Significance: The extrapolation PK/PD/Clinical response model for DDP4 inhibitors was developed and successfully applied to evaluate alternative trial design in pediatric T2DM patients.

1688454

Population Pharmacokinetics of Retosiban Administered Intravenously to Healthy, Pregnant Females With Uncomplicated Preterm Labor Between $30^{0/7}$ – $35^{6/7}$ Weeks Gestation

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Statement of Purpose, Innovation or Hypothesis: Retosiban is an oxytocin receptor antagonist being developed for the treatment of preterm labor (PTL). Preterm birth (PTB), frequently preceded by PTL, is the largest single cause of infant morbidity and mortality. The aim of this analysis was to describe the popualtion pharmacokinetics (PPK) of retosiban in pregnant women with uncomplicated preterm labor between $30^{0/7}$ – $35^{6/7}$ weeks gestation.

Description of Methods and Materials: This was a randomized, double blind, placebo controlled, dose-ranging study conducted in 3 parts (A,B and C). Pregnant women in PTL between 30 0/7 and 35 6/7 weeks of gestational age were eligible. For Parts A and B, patients received either active IV retosiban or IV placebo for 12 hours. In Part C, patients received either retosiban IV or placebo IV for 48 hours. Total N on active therapy = 44. Plasma samples were analyzed for retosiban using a validated method based on protein precipitation, followed by HPLC/MS/MS analysis. The lower limit of quantification (LLQ) was 1 ng/mL with a higher limit (HLQ) of 1000 ng/mL. NONMEM 7.2.0 was used for the analysis. R 2.13.0 was used for all diagnostic plots, bootstrap datasets and summary statistics. Model evaluation was performed using bootstrapping and visual predictive check (VPC).

Data and Results: The final model is shown in the Table. Retosiban is rapidly cleared via CYP3A4 in pregnant women and induces its own metabolism. No covariates (race, ethnicity, age, or gestational age) had any effect on the PPK of retosiban. All parameters were reasonably precise, except for V1. VPC analysis showed that the model was predictive.

Interpretation, Conclusion or Significance: The PPK of retosiban are adequately described by a two compartment model with induction of clearance modeled over time. The induction is not clinically significant. No covariates tested had any effect on the disposition of retosiban.

1688454: Summary of Final Model

Parameter	Mean [%RSE] (95% CI)	BSV (%) [%RSE] (95% CI)
CLss (L/hr)	86.5 [4.1] (79.4, 93.5)	17.3 [24.0] (11.2, 24.3)
CLint	66.9 [5.1] (59.8,73.5)	
V1 (L)	19.0 [26.8] (9.6, 50.1)	65.8 [55.7] (0.01,152)
V2 (L)	48.0 [11.8]	ne
Q (L/hr)	39.8 [17.9] (15.5,76.5)	ne
σ	18.8% [24.7] (14.2,23.1)	70.8 [45.6] (28.8, 93.2)

CLss - steady state CL CLint - initial CL BSV -between-subject variability

1700523

Trends in Pregnancy Labeling and Data Quality in USApproved Pharmaceuticals

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Statement of Purpose, Innovation or Hypothesis: Determination of drug safety in pregnancy and dissemination of data have continued to present challenges to industry, regulatory agencies, and providers. Over the past decade, there have been efforts made to improve drug labeling for pregnancy and lactation. This included recommendations for a new format for pregnancy labeling in 2008. The purpose of this study was to describe trends in pharmaceutical labeling for pregnancy and lactation over time.

Description of Methods and Materials: The labeling data of 213 new molecular entities (NMEs) approved between January 2003 and December 2012 were systematically reviewed. Initial approval data and subsequent labeling revisions were evaluated for pregnancy category, source of pregnancy data, presence of a pregnancy registry, data in labor and delivery, and the quality of breast feeding data. Utilization of the new labeling format was also recorded.

Data and Results: The most commonly approved pregnancy category was "C" (51.6%). The majority of drugs (92.9%) had pregnancy data based on animal studies and 5.2% had human pregnancy data. There was no mention of drug use in labor and delivery in 73.7% of labels, while12.2% mentioned labor and delivery, but reported there was no data. Only 2.8% of medications had human data, with the remainder having animal data. For breast feeding, there was no data in 47.9% of labels, animal data in 42.7%, and human data in 4.7%. The majority of medications (85%) did not have a pregnancy registry. Of those that did, 31.3% were agent-specific and 68.7% were by therapeutic category. Since the new labeling recommendations, 4.7% of medications incorporated the new format into the labeling, primarily approvals that occurred in 2012. There were no significant changes in the other parameters over time.

Interpretation, Conclusion or Significance: Informed and safe drug use during pregnancy can be a major determinate of maternal and fetal outcomes. Despite significant efforts to improve drug labeling for pregnancy and lactation, there remains a paucity of human data in this under-studied population.

1702271

Succinylcholine or Rocuronium for Emergency Pediatric Tracheal Intubation?

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Statement of Purpose, Innovation or Hypothesis: Rapid sequence intubation (RSI) and modified rapid sequence intubation (MRSI) are established practice in emergency pediatric tracheal intubation. With the standardization of protocols for securing the pediatric airway, the direct availability of muscle relaxant of choice may differ. This survey included a questionnaire regarding muscle relaxants and their use for RSI and/or MRSI in the pediatric population.

Description of Methods and Materials: This descriptive study consisted of a survey of pediatric anesthesiologists, who have completed training and are active members of the Society for Pediatric Anesthesia (SPA). It was submitted to and approved by the SPA research committee and sent by electronic mail to active members. Responses were compiled and analyzed to identify the technique and medications used for emergency tracheal intubation in children.

Data and Results: The mean SD years in practice of the 228 respondents was 14.9 8.16 years, with pediatric patients comprising 77 33% of their practice. 76.8% completed a fellowship in pediatric anesthesia. 60% of the respondents' practice setting was at a Children s Hospital. Indications of use of a MRSI were a concern about apnea time tolerance with traditional RSI, concern about muscular pathology if succinylcholine is used and concern about airway difficulty in 73.7%, 70% and 44.2% of respondents, respectively. The muscle relaxant of choice for a RSI in a pediatric patient was succinylcholine (62.2%), followed by rocuronium in 22.1% of respondents. The muscle relaxant of choice was rocuronium (62.7%), followed by succinylcholine in 12.4% of respondents who used the MRSI technique. The age of the patient was considered as a factor in choosing the muscle relaxant (i.e. concern about an undiagnosed neuromuscular pathology) in 35% of respondents using the MRSI technique.

Interpretation, Conclusion or Significance: Technique of a MRSI varies amongst pediatric care providers. Rocuronium is the muscle relaxant more often associated and used with modified rapid sequence induction

1709161

Pharmacokinetics (PK), Pharmacodynamics (PD) and Safety Profile of AMG 181 (MEDI7183) in Healthy Japanese are Not Different From Caucasian Subjects

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Statement of Purpose, Innovation or Hypothesis: AMG 181 is a human anti-α4β7 antibody in Phase 2 development for treating Crohn's disease (CD) and ulcerative colitis (UC). This ongoing Phase 1 study was designed to evaluate safety, tolerability, immunogenicity, and PK/PD of single subcutaneous (SC) dose of AMG 181 in healthy Japanese subjects (HJS) and Caucasian subjects (HCS).

Description of Methods and Materials: In this randomized, double-blinded, placebo-controlled, ascending single-dose study, 24 male HJS were randomized 6:2 to receive a single SC dose of AMG 181 (21, 70, or 210 mg) or placebo. 8 male HCS were randomized 6:2 to receive AMG 181 (70 mg) or placebo. AMG 181 concentration, anti-drug antibodies (ADA), α4β7 receptor occupancy (RO) and CD4+ T cell counts were assessed.

Data and Results: The α4β7 RO on CD4+ naïve T cells was maintained at >90% for at least 4, 8, and 8 weeks at 21, 70, and 210 mg SC, respectively. The AMG 181 PK/PD profiles, as well as Cmax and AUC(0–4weeks) values under 70 mg SC were not different between HJS and HCS. Further, the AMG 181 PK/PD profiles were super-imposable between this study and those from non-Japanese subjects from the first-in-human study (NCT01164904). So far, no subjects tested ADA positive at 1 and 3 months after dosing. Blinded safety data to date have shown safety and tolerability profiles of single SC administration of AMG 181(up to 210 mg) or placebo in Japanese and Caucasian healthy subjects are acceptable.

Interpretation, Conclusion or Significance: The AMG 181 safety, immunogenicity, and PK/PD properties under single fixed SC dosing regimens are not different among healthy Japanese, Caucasian, and non-Japanese subjects. These data suggest that Japanese subjects can be enrolled in AMG 181 global clinical trials for CD and UC.

1710472

Chronic Pain Management With Oxycodone DETERx of Patients With Dysphagia

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Encore Presentation: *In vivo pharmacokinetic data is latest data and not presented before; some portions of in vitro data was presented at 1. Kopecky EA, Varanasi RK, Fleming AB, Saim S, Mayock SP. Alternative methods of oxycodone DETERx administration. Poster presented at the American Association of Pain Management Annual Meeting, September 2012, Phoenix, AZ 2. Varanasi RK, Fleming AB, Saim S. Alternative methods of oral administration for oxycodone DETERx, a novel, extended-release, tamper-resistant opioid formulation. Poster presented at Annual Meeting of the American Association of Pharmaceutical Scientists, October 2012, Chicago, IL*

Statement of Purpose, Innovation or Hypothesis: Chronic pain treatment can be complicated in patients (children, adults, elderly) with problems swallowing solid, extended-release (ER) formulations, due to dysphagia/odynophagia. Purpose: to demonstrate *in vitro* equivalence between administering oxycodone DETERx ER, abuse-deterrent, multi-particulate formulation (beads) as intended or via alternate oral routes - opening the capsule and sprinkling onto soft foods or administering through enteral tubes; to show *in vivo* that oxycodone DETERx beads can be chewed without compromising the ER mechanism

Description of Methods and Materials: Feeding tube study: beads (40mg) were transferred via nasogastric & gastrostomy tubes using different vehicles directly into a dissolution vessel. Soft food study: beads were poured onto soft food, mixed, and held in contact for 0, 30, 60 minutes; mixtures were poured into separate dissolution vessels. A control sample was tested. Mean dissolution data of test and control were compared using the FDA-recommended similarity factor (f2). Pharmacokinetic study: ~40 subjects were studied in a randomized, open-label, active-controlled, cross-over study to assess chewing beads on oxycodone blood levels. Blood samples were analyzed by LC-MS/MS. Pharmacokinetic parameters (C_{max}, AUC_{INF}) were calculated using non-compartmental analysis. Adverse events, oxygen saturation, vital signs, clinical labs were monitored.

Data and Results: *In vitro*; f2 value was >50, indicating samples administered via feeding tubes and control had similar dissolution profiles. $f2 > 50$ was obtained when dissolution of sprinkled beads was compared to control, irrespective of hold time. *In vivo*; chewing beads did not increase C_{max} relative to intact beads (C_{max} LSM ratio:0.90); the concentration-time curve was similar for oxycodone DETERx chewed and intact (AUC_{INF} LSM ratio of 1.02); the mean individual subject C_{max} ratio of LSMs for oxycodone DETERx was lower than that of published OxyContin OP data (0.9 v.1.71, respectively). The safety profile was similar between treatments.

Interpretation, Conclusion or Significance: Oxycodone DETERx may be administered using alternative oral routes of administration (nasogastric or gastrostomy tubes) and sprinkling onto soft food. Chewing does not increase oxycodone blood levels. Oxycodone DETERx may offer patients and physicians an alternate means of treating chronic pain with dysphagia.

1710686

Developmental Pharmacogenomics of Transporters ABCB1 (MDR1) and ABCC2 (MRP2) in Pediatric Liver

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Statement of Purpose, Innovation or Hypothesis: To investigate the effect of genetic polymorphisms on the ontogeny of protein expression of ABCB1 and ABCC2 in human pediatric liver.

Description of Methods and Materials: We have previously reported on the age-associated relative protein expression of the transporters ABCB1 and ABCC2 in pediatric livers using Western blotting with GAPDH as reference gene (Clin Pharmacol Ther 2007, 81, S101). From 69 of these specimens, genomic DNA was isolated and analyzed for functionally relevant single nucleotide polymorphisms in ABCB1 (C3435T, C1236T, G2677T/A) and ABCC2 (C3972T, G1249A, and C24T) using the TaqMan assay. Groups were stratified according to genotype and donor age quartile, and statistical analysis was performed by one-way and two-way ANOVA with weighted least squares.

Data and Results: For ABCC2, protein expression for polymorphism C3972T was significantly increased in specimens with TT genotype (TT vs. CT: $p = 0.0035$; TT vs. CC: $p = 0.0293$). In the youngest age quartile (median: 0.11 years; range 0–0.16), relative expression was on average 3.04-fold higher in TT vs. CC genotype and 2.67-fold higher in TT vs. CT genotype. Similarly, in the oldest age quartile (median: 8.9 years, range: 6.01-12.0), relative expression was on average 2.03-fold higher in TT vs. CC genotype and 2.23-fold higher in TT vs. CT genotype. Genotype-dependent differences in ABCC2 expression in age quartiles 2 (median: 0.20 years; range: 0.17–0.30) and 3 (median: 1.28 years; range: 0.31–6.0) did not reach statistical significance, most likely because of imbalanced genotype distribution in these groups combined with small sample size. The polymorphisms G1249A and C24T of ABCC2 as well as C3435T, C1236T, and G2677T/A of ABCB1 did not significantly affect the relative protein expression of the respective transporter.

Interpretation, Conclusion or Significance: This study suggests that the effect of C3972T on the protein expression of ABCC2 is conserved throughout the postnatal ontogeny of this transporter and contributes to the intrinsic variability in ABCC2 expression observed in the investigated specimen set.

1716442

Body Surface Area-based Dosing Approach Produced Comparable Golimumab Exposure Across Different Age Ranges After Subcutaneous Administration of Golimumab in Pediatric Patients with Juvenile Idiopathic Arthritis

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Statement of Purpose, Innovation or Hypothesis: To evaluate the pharmacokinetics (PK) of body surface area (BSA)-adjusted dosing of SC golimumab 30 mg/m^2 every 4 weeks (q4w) + methotrexate (MTX) in pediatric patients with juvenile idiopathic arthritis (JIA) and to determine the similarity in golimumab exposure between these patients and adult rheumatoid arthritis (RA) patients following SC administration of 30 mg/m^2 or 50 mg fixed dose q4w, respectively.

Description of Methods and Materials: A dosing regimen of SC golimumab 30 mg/m^2 (maximum 50 mg) q4w + MTX in pediatric patients with JIA was predicted to be equivalent to SC golimumab 50 mg q4w + MTX in adult RA patients. GO-KIDS is a randomized-withdrawal, double-blind, placebo-controlled, parallel-group, multicenter Phase 3 trial of SC golimumab 30 mg/m^2 (maximum 50 mg) q4w + MTX in pediatric patients aged 2 to <18 years old with active JIA

despite current MTX therapy. PK, safety, and efficacy evaluations were performed every 4 weeks. Serum golimumab trough concentrations for 119 patients were determined via a validated, specific and sensitive immunoassay at weeks 0, 4, 8, 12 and 16 and were summarized by age.

Data and Results: Treatment with SC golimumab 30 mg/m^2 q4w resulted in median trough serum golimumab concentrations of 1.05 to 1.28 μg/mL at steady state in three different age groups of JIA patients (Table). The steady-state trough concentrations in patients with JIA were similar to that seen in adult RA patients (median: 0.93 μg/mL; mean [SD]: 1.17 [0.99] μg/mL) who received golimumab 50 mg + MTX.

Interpretation, Conclusion or Significance: The study results confirmed that serum golimumab exposure in pediatric patients with JIA following administration of 30 mg/m^2 q4w was similar to that observed with 50 mg q4w in the adult RA population and was consistent across the various age groups studied.

1716442: Golimumab Trough Concentrations

	<6 Years Old	≥6 to <12 Years Old	≥12 Years Old	Combined
N	17	29	63	109
Mean (SD) (μg/mL)	1.28 (0.620)	1.05 (0.670)	1.10 (0.801)	1.12 (0.740)
Median (μg/mL)	1.34	1.12	1.09	1.15

SD, standard deviation

1666314

Development of a Sensitive LC-MS/MS Method for Analysis of Flaxseed Lignans in Mouse Plasma and Mouse Lung Homogenate

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Statement of Purpose, Innovation or Hypothesis: Dietary whole-grain flaxseed has potent anti-inflammatory, anti-fibrotic and antioxidant properties in murine models of acute and chronic lung injury. Protective properties have been linked in part to its' lignan content. Sensitive assays using small volumes of plasma and other biological matrices such as lung tissue are necessary to investigate pharmacology of bioactive flaxseed lignans and metabolites.

Description of Methods and Materials: We developed a high-performance liquid chromatographic method with tandem mass spectrometry detection (LC-MS/MS) for quantification of lignans [Secoisolariciresinol diglucoside (SDG), secoisolariciresinol (SECO), enterodiol (ED) and enterolactone (EL)] in 100 μL of plasma and 100 μg of lung homogenate. For free lignans, cleanup consisted of protein precipitation, followed by reversed-phase chromatographic separation (high-performance liquid chromatography) and selective detection using electro-spray ionization tandem mass spectrometry. Samples were hydrolyzed with β-glucuronidase, over-night at 37˚C for 18 hours and extracted by liquid-liquid extraction using methyl tertiary-butyl ether and reconstituting the dried samples with 75% acetonitrile in water and analyzed for total ED and EL.

Data and Results: Lignans were analyzed on API 4000 Qtrap in the negative electro-spray ionization mode with optimized MS/MS parameters. A calibration curve was prepared in mouse plasma and mouse lung homogenate for SDG and SECO (5.0 – 2500 ng/mL) and for ED and EL (1.0–1000 ng/mL) was found linear with co-efficient of regression, r2 > 0.99. Samples were extracted by protein precipitation using 100% acetonitrile and analyzed for lignans. Mouse plasma and lung homogenate samples were hydrolyzed with β-glucuronidase and analyzed for total ED and EL.

Interpretation, Conclusion or Significance: This assay provides reliable quantification of lignans in small volumes of plasma and lung homogenate samples and successfully utilized for analysis of samples from a mouse pharmacokinetic study. This assay is also successfully extended for analysis of lignans in human plasma samples. Funded in part by: NIH-R01 CA133470, NIH-RC1AI081251 and NIH-P30 CA016520 (MCS)

1690742

Single-dose Pharmacokinetics of Selexipag, Under Fasting and Non-fasting Conditions, in Healthy Male Subjects

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Statement of Purpose, Innovation or Hypothesis: Patients with pulmonary arterial hypertension (PAH) have a deficiency in prostacyclin and prostacyclin synthase. Thus, targeting the prostacyclin pathway is an effective treatment option for PAH. Selexipag is a novel, orally available, selective prostacyclin receptor (IP) agonist, currently under development for the treatment of PAH. ACT-333679, the active metabolite of selexipag, is also a selective and potent agonist at the IP receptor.

Description of Methods and Materials: In this Phase 1 study, the pharmacokinetics of a single oral dose of 400 μg selexipag were investigated, under fasting and non-fasting conditions, in 12 healthy male subjects, 19–44 years of age. This cross-over study consisted of 2 single-dose periods, separated by a 7-day wash-out. Subjects received selexipag (400 μg), either in the fasted condition or after a high fat breakfast. Blood sampling for pharmacokinetic evaluations and tolerability assessments (clinical laboratory parameters, vital signs, adverse events [AE] and ECG recording) were performed at regular time intervals.

Data and Results: Selexipag C_{max} was 35% lower in the fed condition (4.9 ng/mL) compared to the fasted condition (7.7 ng/mL), whereas AUC was 10% higher in the fed condition (16.06 h*ng/mL versus 14.65 h*ng/mL). Food intake delayed the absorption of selexipag; median t_{max} was increased from 1 hour (fasting condition) to 2.8 hours (fed condition). ACT-333679 C_{max} and AUC were decreased by 48% and 27%, respectively, when selexipag was administered in fed (4.3 ng/mL and 36.79 h*ng/mL) compared to the fasted condition (8.4 ng/mL and 50.75 h*ng/mL). Food intake delayed exposure to ACT-333679; median t_{max} was increased from 2.5 hours (fasted condition) to 4 hours (fed condition). A single oral dose of 400 μg selexipag was well tolerated. The most frequent AE was headache. No treatment-related effects on vital signs, clinical laboratory, and ECG parameters were detected.

Interpretation, Conclusion or Significance: In conclusion, food intake decreased the rate and extent of exposure to ACT-333679 after administration of selexipag.

[Correction added on October 14, 2013, after first online publication: In the original publication the order of the author's names was incorrect. The correct order is Séverine Niglis, Shirin Bruderer, Kaori Okubo, Hideya Mukai, Tim Mant, Jasper Dingemanse]

1699358

A Phase 1 Study to Investigate the Absorption, Metabolism and Excretion of [14C] Migalastat Hydrochloride Following a Single Oral Administration in Healthy Volunteers

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Statement of Purpose, Innovation or Hypothesis: Migalastat HCl (AT1001/GR181413A) is a low molecular weight iminosugar pharmacologic chaperone under investigation as a treatment for Fabry disease. The purpose of this study was to characterize the absorption, distribution, metabolism, and elimination (ADME) profile of [14C]-migalastat in various matrices following a single oral dose administration and to investigate the metabolic fate of migalastat in these matrices.

Description of Methods and Materials: In this Phase I, open-label study [AT1001-014/GSK116435 (NCT01730482)], a total of 6 healthy male subjects each received a single oral dose of migalastat HCl as an aqueous solution containing 150 mg [14C]-labeled migalastat HCl (37 kBq). Blood, duodenal bile, expired air, urine, and fecal samples were collected at specified time points after dosing throughout the period of confinement at the study site for up to 10 days. Safety was assessed throughout the study by monitoring clinical laboratory tests, ECGs, physical examinations, vital signs, and adverse events.

Data and Results: Following oral administration, median plasma tmax was 4 hours and geometric mean t1/2 of elimination was approximately 6 hours for both [14C]-radioactivity and migalastat. The [14C] blood to plasma ratio ranged from 0.76 to 1.12. The majority (59%) of the total radioactivity in plasma was parent compound. Several minor dehydrogenated O-glucuronide conjugated metabolites were identified. Mean urinary and fecal excretion accounted for 77.2% and 20.4% of total [14C]-radioactivity, respectively. No notable radioactivity was detected in bile or expired air. There were no findings of clinical relevance with respect to clinical laboratory results, ECGs, vital signs, physical examination, or body weight measurements.

Interpretation, Conclusion or Significance: Migalastat HCl was well absorbed after oral dosing and was predominantly recovered in human urine predominantly as unchanged migalastat. The majority of the total radioactivity in plasma was parent compound. No major metabolites were identified.

1703161

Assessment of the Sites of Gastrointestinal Absorption of Apixaban in Healthy Subjects

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Statement of Purpose, Innovation or Hypothesis: Apixaban is a direct reversible factor Xa inhibitor approved in multiple countries for prevention of venous thromboembolism in patients following total knee or hip replacement and prevention of stroke and systemic embolism in patients with atrial fibrillation. Apixaban is an orally administered agent with a bioavailability of approximately 50%. This study assessed apixaban relative bioavailability when released in specific regions of the gastrointestinal (GI) tract.

Description of Methods and Materials: This was an open-label, randomized, four-period, four-treatment crossover study in 12 healthy subjects. A single dose of apixaban 2.5 mg solution was administered orally and delivered to the distal small bowel as well as the ascending colon via an Enterion^{TM} capsule. Relative bioavailability of a crushed apixaban 2.5-mg tablet released in the ascending colon via the capsule was also assessed. Capsule location was monitored using scintigraphic imaging, and drug release into the targeted GI region was triggered by radio signal. There was a 7-day washout between treatments. Blood samples were collected up to 60 hours postdose for assay of apixaban concentration. Pharmacokinetic parameters were derived from plasma concentration-time profiles using noncompartmental methods. Analysis of variance was performed on log(Cmax) and log(AUC) to assess the extent of absorption for different regionally delivered doses relative to that following oral administration.

Data and Results: Compared to oral administration, the Cmax and AUC(0-T) of apixaban solution were approximately 60% lower when apixaban was released in the distal small bowel. Apixaban Cmax and AUC(0-T) were 90% and 84% lower, respectively, when apixaban solution was released in the ascending colon. Relative bioavailability (in terms of both Cmax and AUC) of the crushed tablet released in the ascending colon was approximately 60% lower than that of solution released in the colon and approximately 95% lower than solution following oral administration.

Interpretation, Conclusion or Significance: Apixaban exhibits region-dependent GI absorption with limited absorption occurring in the colon. Absorption of apixaban appears to occur primarily in the small intestine and to decrease progressively in the distal GI tract.

1706689

The Influence of Vitamin D and Uremic Toxins on Human CYP3A4 Activity and Expression

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Statement of Purpose, Innovation or Hypothesis: In patients with end-stage renal disease, not only renal clearance but also non-renal clearance containing hepatic clearance is known to be impaired. For example, the concentration of erythromycin, a substrate of cytochrome P450 3A4 (CYP3A4), has been reported to be elevated in patients with end-stage renal disease. This study aimed to elucidate the reason for the decrease in non-renal clearance in patients with end-stage renal disease.

Description of Methods and Materials: Normal and uremic deproteinized sera were used to assess the effects of low-molecular-weight uremic toxins on CYP3A4 activity in an assay of testosterone 6β-hydroxylation in human liver microsomes and P450-GloTMAssays in human LS180 cells. Four uremic toxins (3-carboxy-4-methyl-5-propyl-2-furanpropanoic acid, hippric acid, indole-3-acetic acid, and 3-indoxyl sulfate) present at high concentrations in uremic serum were also studied individually.

Data and Results: Uremic serum (less than 10%) and the individual uremic toxins did not affect testosterone 6β-hydroxylation in human liver microsomes. However, the increased CYP3A4 activity in LS180 cells exposed to normal serum reduced in the presence of uremic serum. CYP3A4 mRNA and CYP24A1 mRNA levels also increased in LS180 cells exposed to normal serum. This effect was reduced in uremic serum-treated cells and in cells exposed to normal serum with uremic toxins added to it. The concentration of 1,25-dihydroxyvitamin D in uremic serum (9.3 ± 1.9 pmol/L) was significantly lower than that in normal serum (62.5 ± 5.0 pmol/L). Addition of 1,25-dihydroxyvitamin D to uremic serum partially restored the serum effect on CYP3A4 expression.

Interpretation, Conclusion or Significance: In conclusion, the present study indicated that the decreased levels of 1,25-dihydroxyvitamin D and the accumulation of uremic toxins contributed to the decreased non-renal clearance of CYP3A4 substrates such as erythromycin.

1707846

Effect of Experimental Kidney Failure on Warfarin Reduction in Rats

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Statement of Purpose, Innovation or Hypothesis: The anticoagulant warfarin is commonly used in chronic kidney disease (CKD) patients. Hepatic Phase I metabolism mediated primarily by CYP2C9, with or without subsequent Phase II glucuronidation accounts for about 85% of total warfarin clearance. Warfarin also undergoes about 15% reduction by hepatic reductases, which generate warfarin alcohols of two diastereoisomers (RS/SR- and RR/SS-warfarin alcohol). Kidney disease affects the non-renal clearance of drugs by modulating the functional expression of drug metabolizing enzymes. The impact of kidney disease on CYPs is well-documented; however, its effect on reductases has not been evaluated. The aim of this study was to assess the effect of experimental kidney failure on warfarin reduction in rats.

Description of Methods and Materials: Microsomal and cytosolic fractions were extracted from liver tissue harvested from 5/6th-nephrectomized and control rats ($n = 3$ per group). Both fractions were incubated with racemic warfarin under optimized conditions, and warfarin alcohols were measured using LC-MS/MS. A Michaelis-Menten model was used to fit the formation of alcohol metabolites, and the total reductase enzyme activity was estimated.

Data and Results: The formation of RS/SR-warfarin alcohol was decreased by 51% ($P < 0.001$) and 56% ($P = NS$) in cytosols and microsomes, respectively in nephrectomized rats compared to controls. The formation of RR/SS-warfarin alcohol was unchanged in both fractions.

Interpretation, Conclusion or Significance: These results suggest that (a) warfarin reduction is stereoselectively altered, and (b) the metabolic activity of hepatic reductases is decreased in experimental kidney failure similar to that previously shown with CYPs. These findings may explain one mechanism associated with altered warfarin dose requirements and response in CKD patients.

1708722

Effect of Food on the Pharmacokinetics of Pradigastat

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Statement of Purpose, Innovation or Hypothesis: Pradigastat (LCQ908) is a diacylglycerol acyltransferase 1 inhibitor being developed for the treatment of chylomicronemia. The effect of food on pradigastat pharmacokinetics was evaluated in two clinical studies.

Description of Methods and Materials: Studies were conducted in healthy volunteers ($N = 24$/treatment) using parallel group designs. In the first study a single dose of 20 mg pradigastat was administered under fasted condition or with high fat (50% by calories) meal. In the second study a single dose of 40 mg pradigastat was administered under fasted condition or with low (15%) or high fat (50%) meal. Blood samples were collected to measure pradigastat pharmacokinetics.

Data and Results: At the 40 mg dose, a high fat meal increased pradigastat Cmax, AUC0-24, AUC0-72, and AUC0-168 by 20%, 12%, 13%, and 18%, respectively, while the low fat meal increased pradigastat exposure by 8%, 9%, 14%, and 18%, respectively. This degree of increase in pradigastat exposure (8–20%) is unlikely to lead to any clinically meaningful difference in pradigastat's efficacy or tolerability profile, as it is lower than the variability of pradigastat pharmacokinetics observed (32–74%). With the 20 mg dose, a high fat meal increased pradigastat Cmax, AUC0-24, AUC0-72, and AUC0-168 by 38%, 60%, 54% and 42%, respectively. The degree of increase in the exposure is still lower than the variability observed (67–87%). Additional modeling is needed to better understand the potential clinical effects of a 38–60% increase in pradigastat seen with 20 mg dose administered with food. Pradigastat was well tolerated in all conditions. Only a few of the subjects enrolled experienced mild gastrointestinal adverse events when pradigastat was administered with a high fat meal.

Interpretation, Conclusion or Significance: Food increases pradigastat plasma exposure, although the fat content of a meal does not appear to alter the overall food effect. The magnitude of increased plasma exposure with food at the 40 mg dose is unlikely to be clinical relevant.

1709713

Effect of Hypothermia on ABCG2- and ABCB1-mediated Drug Transport

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Statement of Purpose, Innovation or Hypothesis: Therapeutic hypothermia, active cooling of a patient to a core body temperature of $32 - 34^{\circ}C$, is a neuroprotective therapy that has been shown to decrease cytochrome P450-based drug metabolism leading to increased drug concentrations. However, it is unknown whether cooling impacts other important components of drug disposition such as drug transporters. We aimed to investigate the effects of hypothermia on the activity of two clinically important efflux transporters, ABCG2 and ABCB1.

Description of Methods and Materials: ABCG2- and ABCB1-overexpressing Madin-Darby canine kidney (MDCKII) cells were grown to confluence on transwells for permeability assays. Vectorial flux of 5 nM [3H]cimetidine, 10 nM [3H]digoxin, and [14C]sucrose was measured to evaluate ABCG2-mediated transport, ABCB1-mediated transport, and paracellular flux respectively by liquid scintillation counting. Experiments were performed at 37˚C and 33˚C (target clinical temperature) and apparent permeability and efflux ratios were calculated.

Data and Results: In ABCG2 overexpressing MDCKII cells, the cimetidine basolateral to apical apparent permeability (Papp,B->A) was $18.9 \pm 2.4\%$ lower at 33˚C (mean ± SD; 16.32 ± 0.61 to 13.23 ± 0.23; $p = 0.0012$). The efflux ratio (Papp,B->A/Papp, A->B) was also significantly reduced by cooling (4.34 ± 0.26 to 3.23 ± 0.55; 25.6% lower; $p = 0.036$). Similarly, in ABCB1 cells, digoxin Papp,B->A was $36.4 \pm 3.5\%$ decreased (34.30 ± 1.27 to 21.81 ± 1.06; $p = 0.0002$). Digoxin Papp,A->B in ABCB1 over-expressing MDCKII cells was consistent with paracellular flux, preventing calculation of ERα.

Interpretation, Conclusion or Significance: In this *in vitro* model of therapeutic hypothermia, a 4˚C reduction in temperature significantly decreased both ABCG2- and ABCB1-mediated flux suggesting that drug disposition may be impacted clinically. To safely use therapeutic hypothermia in patients, it is imperative that potential cooling-induced alterations in drug transporter function is investigated *in vivo*.

1709791

Effects of Fluid Volume on Nifedipine Dissolution and Absorption in Humans

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Statement of Purpose, Innovation or Hypothesis: Immediate release (IR) nifedipine, used for preterm labor, is poorly soluble with highly variable absorption. The purpose of our studies was to evaluate effects of increasing gastric fluid volume on nifedipine dissolution and absorption in humans.

Description of Methods and Materials: Nifedipine dissolution from IR capsules (10 and 20 mg "2 × 10") in 100, 200, and 400 ml Fasted-State-Simulated-Gastric-Fluid (FaSSGF) was determined using a USP-II standardized mini- apparatus. Using the dissolution results, a two-phase randomized crossover single dose pharmacokinetic study in six healthy volunteers was designed to determine the effect of water volume on nifedipine absorption. Subjects received a 10 mg dose of nifedipine IR with 50 or 250 ml water. Blood samples were collected up to 6 hours following dosing and nifedipine plasma concentrations determined using LC/MS/MS. Nifedipine Cmax, tmax, and AUC0-6 were compared using paired t-test.

Data and Results: Faster drug release and delayed precipitation were observed for 200 ml FaSSGF volume (AUCdiss = 51 ± 1.8 vs. 16 ± 2.1 ng.hr/ml in 200 and 100ml, respectively, $P < 0.001$). This effect was less pronounced for 20 mg doses (AUCdiss = 30 ± 7.5 ng.hr/ml for 400 ml vs. 17 ± 2.9 ng.hr/ml for 200 ml, $P = 0.003$). No significant differences were observed in nifedipine pharmacokinetic parameters between the two phases of the clinical study. However, administration of 250 ml of water with nifedipine IR capsule was associated with marked reduction in Cmax variability (CV% = 47% vs. 70%). In three of the subjects a 2-10 fold increase in Cmax was observed in the large volume phase.

Interpretation, Conclusion or Significance: Nifedipine absorption is associated with high inter-individual variability when administered with large fluid volumes. However, the observed variability in nifedipine absorption and Cmax was reduced, warranting the use of large fluid volumes when IR nifedipine is administered for treatment of preterm labor.

1710413

The Excretion Balance and Pharmacokinetics of the JAK2-selective Inhibitor SAR302503 in Healthy Volunteers

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Statement of Purpose, Innovation or Hypothesis: SAR302503 is a JAK2-selective inhibitor in clinical development as a treatment for myelofibrosis. The objectives of this study were to assess the absorption, metabolism and excretion, and describe the safety and tolerability in humans.

Description of Methods and Materials: This was a single-center, open-label study. A total of 6 healthy male subjects between 18 and 45 years of age were enrolled. Subjects received a single oral 200 mg dose of [14C]-SAR302503 (2.775 MBq) in solution. Blood, urine, and fecal samples were collected up to 840 hours and expired-air samples were collected up to 8 hours post dose. Plasma concentrations of SAR302503 were determined by a validated LC-MS/MS method. Radioactivity in plasma, whole blood, urine, and feces was determined using liquid scintillation counting.

Data and Results: Following administration of a single oral dose of [14C]-SAR302503, the overall mean radioactivity recovery rate was 82.1% of the dose. The majority of the dose (76.9%) was recovered in feces, a small proportion (5.2%) in the urine, and negligible levels (near or below the lower limit of quantitation) in the expired air. SAR302503 was absorbed rapidly with a median plasma tmax of 3 hours, and showed a long terminal half-life of 232 hours. Circulating radioactivity peaked at 3 hours post dose. SAR302503 represented approximately 70% of the total circulating radioactivity, indicating the presence of one or more metabolites of SAR302503. The ratio of blood to plasma concentration of radioactivity ranged from 0.615 to 0.753, indicating limited distribution of SAR302503 and/or its metabolites into red blood cells. Oral administration of a single 200 mg dose of [14C]-SAR302503 was well tolerated in the healthy male subjects.

Interpretation, Conclusion or Significance: Following a single oral dose of [14C]-SAR302503, SAR302503 was absorbed rapidly with a long terminal half-life. SAR302503 represented the majority of the total circulating radioactivity. Fecal excretion was the major elimination pathway. (Sponsored by Sanofi)

1710471

Pharmacokinetics and Placental Transfer of Dexmedetomidine in the Pregnant Ewe-Fetus Model

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Statement of Purpose, Innovation or Hypothesis: In an attempt to improve the safety of maternal-fetal anesthesia, anesthetic agents used in pregnant women undergoing surgery are being evaluated. A highly selective α2-adrenoceptor agonist dexmedetomidine (DEX) approved by FDA as a sedative used in ICU may be suitable for maternal-fetal anesthesia. Considering the side effects of hypotension and bradycardia, the impact of DEX on fetuses in utero is not fully understood. The objective of this study was to investigate the maternal-fetal pharmacokinetics (PK) and placental transfer of DEX using the pregnant ewe-fetus model.

Description of Methods and Materials: Eight third-trimester pregnant ewes received a 1 μg/kg loading infusion for 10 min followed by an IV infusion of 1 μg/kg/h for 1 h. Maternal and fetal blood samples were collected from artery and vein at 10 min up to 250 min. DEX concentrations were quantified by our developed and validated LC-MS/MS assay. Non-compartmental PK analysis was performed using WinNonlin. The partition coefficient (KFM = AUCfetus/AUCmother) profile from mothers to fetuses was established.

Data and Results: Large variations were observed in maternal concentrations (CV% = 141.1%) whereas fetal concentrations were consistent (CV% = 48%) during infusion. After infusion, concentrations in arterial and venous blood were similar in mothers, and the same trend was observed in fetuses. DEX concentrations in maternal artery and fetal vein were 815.1 ± 497.2 and 104.4 ± 40.3 pg/ml at 10 min, and 410.7 ± 244.4 and 176.8 ± 89.2 pg/ml at 70 min. Distributions in arterial and venous blood for mothers and fetuses reached equilibrium rapidly. KFM was 0.13 ± 0.10 and 0.13 ± 0.08 at 10 min and 70 min respectively, and reached plateau of 0.20 ± 0.15 at 190 min post infusion. At 250 min, KFM was 0.23 ± 0.14. Half-lives in mothers and fetuses were 65.6 ± 20.2 and 124.5 ± 60.8 min, respectively.

Interpretation, Conclusion or Significance: DEX rapidly crossed the pregnant ewe placenta with the partition coefficient of 23% to fetuses. Half-life in fetuses is longer, approximately twice of that in mothers.

1710474

Distributional Properties of Flaxseed Lignans: Preliminary PBPK Model in Mouse

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Statement of Purpose, Innovation or Hypothesis: The cellular fate of active constituents of dietary wholegrain flaxseed, principally the plant lignan precursor secoisolariciresinol diglucoside (SDG), secoisolariciresinol (SECO), and the mammalian lignans enterodiol (ED) and enterolactone (EL) has not been well characterized. Coupled with efforts to examine the potent anti-inflammatory, anti-fibrotic and antioxidant properties of flaxseed in murine models of acute and chronic lung injury, we have constructed a preliminary physiologically-based pharmacokinetic (PBPK) model.

Description of Methods and Materials: A murine SDG PBPK model was developed in PK-Sim 4.2® (Bayer Technology Services, Leverkusen, Germany) using physiochemical data, along with *in-vitro* and *in-vivo* PK studies.

Data and Results: Physicochemical properties for natural SDG and PBPK model inputs include: high solubility (>18.8 mM; >12.9 mg/L), high plasma stability (100% for 1 hr), high chemical stability (100% in PBS), 5% plasma protein binding, LogD -1.69 ± 0.09 and membrane permeability of <-7 (determined by the Parallel Artificial Membrane Permeability Assay (PAMPA)). SDG (C32H46O16) has a molar mass of 686.7 g/mol. Concentrations of SDG, SECO, ED and EL were measured in mouse plasma and lung homogenate after single oral gavage of SDG at a dose of 2.0 mg in 100μL PBS to C57BL6 WT mice. Mean (n = 3) peak plasma concentrations were 545, 19.6, 37.9 and 47.1 ng/mL for SDG, SECO, ED and EL respectively. Peak lung exposure was good for SDG (>1700 ng/g tissue) and SECO (56.4 ng/g) but below assay quantification for ED and EL. A simple diffusion-limited PBPK model was not adequate to explain the observed data. Incubation studies with murine lung cancer cells examined for evidence of incorporation and conversion of SDG to metabolites confirmed both processes. Hence, by adjusting the PBPK model for cellular uptake considerations, agreement with the observed data can be achieved.

Interpretation, Conclusion or Significance: Future efforts will include scaling the murine model to an adult, human population-based-PBPK model in which simulated dosing requirements to achieve pharmacodynamic targets are explored.

1716359

Biocomparability Assessment of Subcutaneous Delivery of Golimumab by a SmartJect Autoinjector or a Needle and Syringe in Healthy Subjects

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Statement of Purpose, Innovation or Hypothesis: To assess the pharmacokinetic (PK) biocomparability of a single subcutaneous (SC) injection of golimumab 100 mg delivered by either a SmartJect® autoinjector or a standard needle and syringe. The safety and tolerability of golimumab delivered by each of the 2 injection methods were also evaluated.

Description of Methods and Materials: A total of 156 healthy subjects received a single SC injection of golimumab 100 mg delivered to the abdomen by either an autoinjector (n = 77) or a needle and syringe (n = 79). Serial serum samples for the measurement of golimumab concentration were collected and analyzed using a validated immunoassay. Non-compartmental analysis was performed to calculate the PK parameters. Adverse events (AEs), including injection site reactions, were recorded.

Data and Results: A total of 141 subjects (70, autoinjector group; 71, needle and syringe group) met the pre-specified criteria for inclusion in the PK comparability assessment. Following a single SC administration of golimumab 100 mg, mean ± SD C_{max} was 6.63 ± 3.32 and 5.97 ± 3.01 μg/mL, and $AUC_{(0\text{-}49days)}$ was 97.39 ± 43.16 and 88.88 ± 36.85 μgday/mL for the autoinjector group and the needle and syringe group, respectively. The primary analysis in the evaluable PK population showed that the 90% confidence interval (CI) for the ratio of geometric mean $AUC_{(0\text{-}49days)}$ values between the 2 injection methods was 95.17% to 120.55%, which fell within the 80% and 125% range. However, the 90% CI for C_{max} was 96.14% to 127.42%, which fell slightly outside the 80% to 125% range. A post hoc intent-to-treat analysis using data from all 156 subjects demonstrated that the 90% CIs for both C_{max} and $AUC_{(0\text{-}49days)}$ fell within the 80% to 125% range. The proportion of subjects with AEs was slightly higher in the needle and syringe group than in the autoinjector group (49.4% vs. 36.4%) with no injection site reactions in either group.

Interpretation, Conclusion or Significance: The study findings demonstrated that the PK of the two SC delivery methods of golimumab by a SmartJect® autoinjector or a standard needle and syringe was biocomparable.

1708458

Development of a Tissue Distribution Population Pharmacokinetic Model for Azithromycin

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Statement of Purpose, Innovation or Hypothesis: The objective of this study was to characterize azithromycin (AZM) pharmacokinetics in soft tissues and polymorphonuclear leukocytes (PML) in order to determine if clinical resistance development is associated with insufficient free, target site concentrations.

Description of Methods and Materials: AZM (500 mg QD) was administered orally to 6 healthy male volunteers for three days.Total plasma concentrations as well as concentrations in the interstitial space fluid (ISF) of muscle and subcutaneous fat tissue were determined by *in vivo* microdialysis on days 1, 3, 5 and 10. Respective concentrations in PMLs were determined from isolated white blood cells.AZM concentrations were modeled simultaneously in NONMEM 7.2 using a semi-physiological tissue distribution model and by accounting for nonlinear protein binding as well as ionization state at physiological pH in the different tissues. Model performance and parameter estimates were evaluated via goodness-of-fit plots and non-parametric bootstrap (N = 1000).

Data and Results: A semi-physiological population pharmacokinetic model was developed that was able to simultaneously characterize AZM concentrations in plasma (total), PMLs (total) and the ISF of muscle (free) and fat (free) tissue by accounting for differences in ionization at physiological pH in the different tissues and non-specific tissue binding. Calculated unionized AZM concentrations in the cytosol of PMLs (6 ± 1 ng/ml) were comparable to free ISF tissue concentrations, whereas total PML concentrations were more than 1000-fold higher (14217 ± 2810 ng/ml). These clinical findings are reflected in the corresponding model-predicted tissue distribution factors (DFPML

(cytosol) = 52, DFISF(muscle) = 0.55, DFISF(subcutis) = 0.25). AZM was still present in the ISF of muscle (9 ± 3 ng/ml) and subcutaneous fat tissue (4 ± 2 ng/ml) at sub-inhibitory concentrations. Respective model parameter estimates from a single run were in good agreement with the computed median bootstrap values.

Interpretation, Conclusion or Significance: Our findings indicate that the pharmacokinetics of the diprotic base AZM is largely dependent on its ionization-driven distribution into tissues. Slow AZM release from the tissues, particularly from PMLs, is responsible for the long terminal half-life of the drug. AZM's long residence in tissues at sub-inhibitory concentrations may explain clinical resistance development.

1708981

Mechanistic Pharmacokinetic/Target Engagement/Pharmacodynamic Modeling in Deciphering Interplay Between a Monoclonal Antibody and Its Soluble Target

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Statement of Purpose, Innovation or Hypothesis: For monoclonal antibodies (mAbs) against soluble targets, their therapeutic efficacy is theoretically driven by the magnitude and duration of free ligand suppression. However, for ligands with rapid turnover, it can be technically challenging to accurately determine the free ligand concentration in the presence of an excessive amount of therapeutic mAb and antibody-ligand complex. The interplay among such mAbs, targets, and the downstream pharmacodynamic (PD) effects has not been well defined *in vivo*.

Description of Methods and Materials: Using interleukin-6 (IL-6) and an anti-IL-6 mAb CNTO-X, as model compounds, a PK/PD study in cynomolgus monkeys was conducted. A quasi-equilibrium pharmacokinetics (PK)/target engagement (TE) mathematical model was developed to describe the interaction between CNTO-X and IL-6, and an indirect response TE/PD model was developed to describe the concentration-effect relationship between free IL-6 and C-reactive protein (CRP), a downstream PD marker of IL-6 activity.

Data and Results: A PK/TE model was established via simultaneous fitting of total CNTO-X, total IL-6 and free IL-6 profiles following a low dose of CNTO-X. The model well captured the observed data and provided estimation of key model parameters with good precision. The PK/TE model was used to predict free IL-6 profiles at higher CNTO-X doses, where accurate determination of free IL-6 became technically too difficult. The measured free IL-6 levels from the low dose groups and PK/TE model-predicted free IL-6 levels from the high dose groups were used to drive the TE/PD model. The indirect response TE/PD model well captured both CRP elevation and CRP lowering in response to free IL-6 level changes from baseline with a simple linear stimulation function.

Interpretation, Conclusion or Significance: Our results suggest that an integrated bioanalytical and PK/TE/PD modeling approach may be useful to predict efficacious doses and duration of action for mAbs targeting rapid turnover soluble ligands. This proposed theoretical framework may be broadly applicable to the development of mAbs against rapid turnover soluble targets.

1709034

Pharmacokinetic-Pharmacodynamic (PK-PD) and Monte Carlo Simulation (MCS) Analyses of GSK1322322 to Evaluate the Need for Weight-based Dosing and Support Dose Selection for a Phase IIb Lung Infection Study

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Statement of Purpose, Innovation or Hypothesis: Develop a population PK model using Phase I data, and conduct MCS to evaluate the need for weight-based dosing and identify doses for a Phase IIb study.

Description of Methods and Materials: A population PK model was developed based on healthy volunteer data using NONMEM. The model estimates, together with randomly generated body weight (BW) data (46.5 -140kg), were used to simulate individual concentration-time profiles over two dosing intervals at steady-state for 5000 subjects per bid dosing regimen, using Trial Simulator. AUC(0-24) and free AUC (fAUC) were determined from each profile. Preclinical fAUC target values were 18 and 26 μg.h/mL which corresponded to 1-log and 2-log declines in bacterial counts in animal infection models. A dose was determined to be acceptable when ≥90% of simulated fAUC values exceed the preclinical targets as this equates to ≥90% target attainment rate (TAR).

Data and Results: Data were best described by a two-compartment model with BW as a covariate on clearance (CL) up to a BW of ~65 kg. A range of potential IV/oral doses were evaluated by MCS. The majority of regimens had both BW groups (<65 or ≥65 kg) simultaneously succeed or fail to achieve a fAUC target. For regimens in which only the low BW group succeeded, the incremental dose increase for the high BW group to achieve the target does not appear to be large enough to warrant a more complicated weight-based dosing scheme. The IV/oral switch doses estimated to meet the preclinical targets were 800mg/1250 mg and 1200 mg/2000 mg, respectively, administered twice daily.

Interpretation, Conclusion or Significance: A population PK model was developed for GSK1322322. Based on the small difference in dose required to have ≥90% TAR across BW groups, weight-based dosing is not necessary. IV/oral dose pairs of 800mg/1250 mg and 1200 mg/2000 mg have been chosen for administration in the Phase IIb lung infection study.

1709146

Impact of Gender on Pharmacokinetics of Intranasal Scopolamine

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Statement of Purpose, Innovation or Hypothesis: An intranasal gel dosage formulation of scopolamine (INSCOP) was developed for the treatment of Space Motion Sickness (SMS), which is commonly experienced by astronauts during space missions. The bioavailability and pharmacokinetics (PK) were evaluated under IND guidelines. Since information is lacking on the effect of gender on the PK of Scopolamine, we examined gender differences in PK parameters of INSCOP at three dose levels of 0.1, 0.2 and 0.4 mg.

Description of Methods and Materials: Plasma scopolamine concentrations as a function time data were collected from twelve normal healthy human subjects (6 male/6 female) who participated in a fully randomized double blind crossover study. The PK parameters were derived using WinNonlin. Covariate analysis of PK profiles was performed using NONMEN and statistically compared using a likelihood ratio test on the difference of objective function value (OFV). Statistical significance for covariate analysis was set at $P < 0.05$ ($\Delta OFV = 3.84$).

Data and Results: No significant difference in PK parameters between male and female subjects was observed with 0.1 and 0.2 mg

doses; however, CL and Vd were significantly different between male and female subjects after the 0.4 mg dose. The results were shown in Table 1. Results from population covariate modeling analysis indicate that a one-compartment PK model with first-order elimination rate offers best fit for describing INSCOP concentration-time profiles. The inclusion of sex as a covariate enhanced the model fitting ($\Delta OFV = -4.1$) owing to the gender-dependent CL and Vd differences after the 0.4 mg dose.

Interpretation, Conclusion or Significance: Statistical modeling of scopolamine concentration-time data suggests gender-dependent pharmacokinetics of scopolamine at the high dose level of 0.4 mg. Clearance of the parent compound was significantly faster and the volume of distribution was significantly higher in males than in females, As a result, including gender as a covariate to the pharmacokinetic model of scopolamine offers best fit for PK modeling of the drug at higher doses.

1709146: Table 1

Parameters (Mean ± SE)	Individual Estimation, Dose = 0.4 mg, Male	Individual Estimation, Dose = 0.4 mg, Female	P value
N	6	6	
V(L/kg)	14.77 ± 3.0	6.72 ± 1.24	0.03
Cl(L/hr/kg)	6.78 ± 0.68	4.29 ± 0.69	0.03

1709467

Population Pharmacokinetics of Brodalumab in Adults with Psoriatic Arthritis From a Multiple Subcutaneous Dose Study

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Statement of Purpose, Innovation or Hypothesis: Brodalumab is a human IgG2 anti-interleukin-17 receptor A (anti-IL-17RA) monoclonal antibody that selectively targets human IL-17RA, thus inhibiting biological activity of IL-17A, IL-17F, IL-17A/F, and IL-25. To characterize pharmacokinetics (PK) of brodalumab in subjects with psoriatic arthritis (PsA) and evaluate the effect of covariates on the PK, a population pharmacokinetic (popPK) analysis of Phase 2 data of brodalumab in subjects with PsA was conducted.

Description of Methods and Materials: PK data were from a randomized, double-blind, placebo-controlled, multiple-dose study in subjects with PsA to evaluate the safety, tolerability and efficacy of brodalumab. A 2-compartment popPK model with parallel linear and non-linear elimination pathways was fit to PK data of brodalumab 140 and 280 mg Q2W using nonlinear mixed-effect modeling approach. The final model was evaluated using standard diagnostic plots and visual predictive checks.

Data and Results: The final 2-compartment model with first-order absorption and parallel linear and non-linear elimination was able to describe the observed PK data well. The population typical values for CL, Vc and Vmax were 0.383 L/d, 5.67 L, and 5.88 mg/d, respectively, and were similar to those estimated in subjects with psoriasis or asthma. Covariate analysis showed total body weight was both a statistically and clinically significant covariate on brodalumab PK, with effect exponents on CL, Vc and Vmax of 1.01, 0.89, and 0.87, respectively. After accounting for the covariate effects, there was still substantial unexplained BSV on these parameters, with estimates of 43.4, 108, and 27.3% CV for CL, Vc, and Vmax, respectively. Model parameters were estimated precisely with %RSE of fixed effect parameters, random effect parameters, and covariate effect exponents less than 17%, 25% and 26%, respectively. Shrinkage for all estimated parameters was less than 30%, indicating the model would be appropriate for use in sequential PK/PD modeling.

Interpretation, Conclusion or Significance: The PK of brodalumab was well characterized by the final popPK model and weight was identified as an important covariate explaining some of the population variability of brodalumab PK.

1710299

Predicting the Clearance of CYP3A4 Probe Substrates in Pediatric Populations: A "Bottom-up" Approach vs. "Top-down" Recognition of Covariates

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Statement of Purpose, Innovation or Hypothesis: Drug clearance is an important pharmacokinetic parameter for determining age-dependent differences in drug dosage regimens between adults and children. Accurate clearance scaling to children could be achieved by a physiologically-based "bottom-up" modeling and simulation approach. This requires prior knowledge of adult clearance mechanisms, physiological development and the development of the drug metabolizing enzymes. Clearance can be also extrapolated from adults to children in a refined "top-down" approach which uses size and age as covariates. In this study, the "bottom-up" paradigm is compared with the "top-down" clearance maturation model for CYP3A4-mediated metabolism. Alfentanil and midazolam are used as model drugs.

Description of Methods and Materials: Using *in vivo* adult clearance value, *in vitro* enzyme ontogeny data and age-dependent regression functions in physiological development, a physiology model for the ontogeny of CYP3A4 clearance was developed. Clearance values of alfentanil and midazolam were predicted for a virtual pediatric population aged from day 0 to 18 years old. Clearance predictions for midazolam and alfentanil were compared against literature values. In "top-down" approach, the clearance maturation model (Eq.1) based on body weight and age were constructed from published CL estimates after intravenous administration in both adults and children. Curve fitting was performed using nonlinear mixed effects models. $CLi = CLstd \times (Wi/70)^{0.75} \times PCA^{\theta}/(Tcl^{\theta} + PCA^{\theta})$ Eq.1

Data and Results: There was excellent correlation between observed and predicted clearances for alfentanil ($r = 0.815$) and midazolam ($r = 0.953$) using the physiologically-based approach. The maturation parameters for midazolam and alfentanil from population were estimated. Predicted CL changes with age based on this approach were in close agreement with the PB-based model predictions.

Interpretation, Conclusion or Significance: The outcomes of the "bottom-up" and "top-down" approaches are comparable, in which the clearance maturation using body weight and age as covariates are consistent with the maturation of CYP3A4 pathway that is derived from a mechanistic liver ontogeny model. This demonstrates the value of incorporating the mechanistic *in vitro in vivo* extrapolation (IVIVE) relationship into a population pediatric PK model.

1710404

Can the Subgroup of Metastatic Breast Cancer Patients With Lower Exposure and Potential Shorter Survival Benefit From a Higher T-DM1 Dose?

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Statement of Purpose, Innovation or Hypothesis: On February 22, 2013, the U. S. Food and Drug Administration approved ado-trastuzumab emtansine (T-DM1, KADCYLA™) 3.6 mg/kg administered intravenously once every three weeks for the treatment of patients with HER2-positive metastatic breast cancer (MBC). Exposure-Response (E-R) analyses were performed by the FDA to assess the adequacy of the dose in MBC patients.

Description of Methods and Materials: E-R analyses for efficacy and safety were conducted using data from a randomized, open-label, active-control trial in patients with HER2+ MBC. Cycle 1, Day 21 T-DM1 trough concentrations (Cmin,C1D21) from 68% patients (334/490) were estimated from the population PK model. Kaplan-Meier survival analysis was performed with patients stratified according to median Cmin,C1D21. Multivariate Cox-proportional hazard analysis was performed to determine if exposure was associated with efficacy after adjusting for baseline risk factors.

Data and Results: E-R efficacy analyses (overall survival (OS), progression free survival, and objective response rate) indicated that after adjusting for baseline risk factors, higher T-DM1 exposures are associated with improved OS. The patients with Cmin,C1D21 lower than median value had comparable OS to the active control arm (see Figure). The percentage of patients who received T-DM1 dose adjustments was similar across the exposure range.

Interpretation, Conclusion or Significance: The E-R findings demonstrated that there may be an opportunity to optimize the KADCYLA dose in a subgroup of patients with lower exposures to improve efficacy. The E-R analysis was pivotal for generating a post-marketing commitment to further evaluate E-R for efficacy and safety, utilizing data from an ongoing trial. Results from this analysis may determine the need for a trial to explore dose optimization for patients who have lower exposures on the approved dose.

1710545

A New Simulation Model to Assess the Power of Pharmacodynamic Crossover Studies Conducted to Establish Bioequivalence of Orally-inhaled Drug Products

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Statement of Purpose, Innovation or Hypothesis: To develop a clinical trial simulation model suitable to evaluate the feasibility of Pharmacodynamic(PD) bioequivalence(BE) studies of generic orally inhaled drug products(OIDP's) by (1) incorporating variability of the biomarker (exhaled nitric oxide (FeNO), sputum eosinophils, methacholine challenge) in defined patient populations and to predict their response to OIDP's, (2) applying a bootstrap based non-parametric approach to construct distributions of relative bioavailability (FDS) for test(T) vs. reference(R) formulations, (3) performing power calculations.

Description of Methods and Materials: Crossover studies were simulated with various sample sizes and doses of R and T OIDP's with identical variability. The mean biomarker responses were obtained from an Emax model with relevant parameters for high and intermediate responders. Within-subject and between-subject variability estimates were obtained from literature. Biomarker values from each simulated dataset were analyzed using a linear mixed effects model. The study power was defined as the % of simulated datasets (200) showing bioequivalence (90%CI of FDS is within 0.8-1.2) was calculated via bootstrap procedure.

Data and Results: For FeNO crossover studies, highest power was achieved when the test dose is close to ED50. 90% power was obtained in high responders using sample size of 128 subjects, whereas in intermediate responders it was 50% with the same number of subjects. 90% power was obtained using 32 and 128 subjects in the low variable and the high variable populations respectively. Similar results were obtained for BE studies of other OIDP's.

Interpretation, Conclusion or Significance: The proposed clinical trial simulation model is a useful tool to perform power calculations for curvilinear dose response relationships. PD approach for establishing BE of OIDP's seems feasible in terms of the sample sizes only when 1) Study population consists of high responders and are less variable, 2) Test dose is close to the estimated ED50 value of the drug and biomarker combination, 3) BE criteria are relaxed. Most of the generic formulations have doses much larger than the relevant ED50 values warranting large sample sizes to demonstrate BE. Simulations suggest that it will be a challenge performing BE studies for corticosteroids using FeNO/sputum eosinophils, while the methacholine challenge is a viable pulmonary bioassay for beta-2 agonists.

1716787

Estimation of Population Pharmacokinetic Parameters of Tenofovir Using Unreliable Dosing Histories

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Statement of Purpose, Innovation or Hypothesis: MTN-001 is a multi-center, open label, 3 way cross over study comparing oral, vaginal and combination (oral and vaginal) administration of tenofovir in healthy women. Self-reported adherence in this study was high (94%), but serum concentrations indicated only 64% of participants used tablets consistently. Objective of this analysis was to develop a population pharmacokinetic model (PPK) for tenofovir without using unreliable patient reported dosing records.

Description of Methods and Materials: Plasma samples were collected at the end of each period at pre-dose, 1,2,4,6 and 8 hours in US sites and a pre-dose and a random sample (1–7 hours post dose) in the African sites. A pre-dose sample was also collected at mid-period (3-week) research clinic visits. At each clinic visit, the patients reported the times of the previous 3 doses. Plasma samples were analyzed using a validated UPLC-MS/MS method (LLOQ = 0.3 ng/ml). A method based on superposition (Gupta et al) was applied to develop the model considering only the reliable clinic visit dosing information. This was achieved by estimating a parameter for pre-dose concentration (C0) and linking temporally to the post-dose pharmacokinetic profile by virtue of sequential time. Model development was conducted using NONMEM (v 7.2).

Data and Results: The final dataset included 100 subjects with 474 observation records. Only end of oral treatment visit data was used for modeling. A 2 compartment model with lag time best described the data. Race was a significant covariate on the C0 parameter and not a significant covariate on clearance. There were no trends observed in the basic goodness of fit plots. The VPC showed that the model described the observed data well. Typical estimates of first order absorption rate constant (hr-1), clearance (L/hr), volume of central compartment (Vc), volume of peripheral compartment (Vp) and intercompartmental clearance (L/hr) were estimated as 7.65, 40.7, 293, 498 and 137, respectively.

Interpretation, Conclusion or Significance: The application of Gupta's method for estimating pharmacokinetic parameters from the unreliable patient reported dosing was successful. Pre-dose concentration differences between races could potentially be a result of non-adherence.

1716799

Assessment of Adherence to Tenofovir Oral Administration Using Simulation Strategies

Ayyappa Chaturvedula[1], Michael J. Fossler[2], Craig Hendrix[3]

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Statement of Purpose, Innovation or Hypothesis: MTN-001 is a multi-center, open label, 3 way cross over study comparing oral, vaginal and combination (oral and vaginal) administration of tenofovir in healthy women. Self-reported adherence in this study was high (94%), but serum concentrations suggest that only 64% of participants used tablets consistently. Objective of this analysis is to retrace patient dosing history using pharmacokinetic simulations conditioned on protocol design constraints.

Description of Methods and Materials: Empirical bayesian estimates from a previously developed population PK model were used for simulations. Based on its ~17 hr t½ of tenofovir and QD dosing, retracing was limited to 3 doses prior to the clinic visit. Steady state plasma concentration post 12 hour dose, an expectation of time post dose for pre-dose concentration, was simulated using one of the eight adherence scenarios 000,001,011,100,101,110,010 and 111 (1 -dose taken, 0- dose missed). It was assumed subjects were taking doses at the same times of the day. All the scenarios with simulated concentrations within 60-140% (normal distribution assumption, 20% CV) of the observed pre-dose concentrations were selected as most likely scenarios of dose taking. Trial simulations (Trial Simulator®) were conducted using built-in one coin and two coin models for understanding the impact of non-adherence on Cmin.

Data and Results: A total of 79 subjects out of 100 in this dataset had traceable dosing sequence (one of eight adherence scenarios) within the 60–140% criteria. More than one dosing scenario fits this criteria making the retracing process unsuccessful. Even under very liberal criteria (e.g., labeling an individual as fully adherent if the 111 simulation results are within 60–140% of the observed data) suggests that only 51% of subjects may have a chance to be fully adherent to therapy during the previous three dosing intervals. Trial simulations with full adherence assumption predict a median Cmin of 68 ng/ml and non-adherence at 25% resulted in 37–51% reduction in Cmin using one coin and two coin models, respectively.

Interpretation, Conclusion or Significance: Steady state concentrations by themselves do not allow a precise re-tracing of an individual's recent dosing history, as there is considerable overlap among candidate regimens.

1704468

Utility of Intravenous Midazolam (MDZ) Partial Area-under-the-curve (AUC) to Predict Hepatic Cytochrome P450 (CYP) 3A Activity During Inhibition and Induction

Joanna C. Masters[1], Denise M. Harano[1], Howard E. Greenberg[2], Shirley M. Tsunoda[1], In-Jin Jang[3], Joseph D. Ma[1]

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Statement of Purpose, Innovation or Hypothesis: Midazolam is a preferred CYP3A probe and its systemic clearance (CL) is a phenotypic indicator of hepatic CYP3A activity. Past studies have explored alternative methods to determine MDZ CL. We conducted a retrospective data analysis to determine if partial AUCs could reliably predict MDZ CL during conditions of CYP3A inhibition and induction.

Description of Methods and Materials: Intravenous MDZ plasma concentrations during CYP3A inhibition (n = 40) and induction (n = 33) were obtained from five previous studies in healthy adults. Non-compartmental analysis was performed to determine observed CL and partial AUCs. Linear regression equations were derived from dose-normalized, log-transformed partial AUCs, and predicted CL was determined from these equations during CYP3A inhibition and induction. Preset criterion for linear regression analysis was $r^2 \geq 0.9$. Back-transformed predicted CL was compared to observed CL, and relative bias and precision were assessed using percent mean prediction error (%MPE) and percent mean absolute error (%MAE), respectively.

Data and Results: During CYP3A inhibition, all evaluated partial AUCs did not meet criterion of $r^2 \geq 0.9$. During CYP3A induction, predictive equations for partial AUCs from 0 to 1 hour (AUC_{0-1}), AUC_{0-2}, AUC_{0-4}, and AUC_{0-6} were acceptable, with good precision and minimal bias.

Interpretation, Conclusion or Significance: During conditions of CYP3A induction, but not CYP3A inhibition, midazolam AUC_{0-1}, AUC_{0-2}, AUC_{0-4}, and AUC_{0-6} reliably predicted systemic clearance, and consequently hepatic CYP3A activity in healthy adults.

1704468: Table

AUC interval	r^2 (≥0.9)	Mean Predicted CL (L/h)	% MPE (-15% to +15%)	% MAE (<15%)
INDUCTION		*Mean Observed CL (L/h) = 49.75*		
AUC_{0-1}	0.92	48.84	0.97	12.23
AUC_{0-2}	0.97	49.25	0.41	7.89
AUC_{0-4}	0.99	49.50	0.14	4.51
AUC_{0-6}	>0.99	49.63	0.05	2.37

1704520

Intravenous Midazolam Partial Area-under-the-curve as a Biomarker to Predict Hepatic Cytochrome P450 3A Baseline Activity in Healthy Subjects

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Statement of Purpose, Innovation or Hypothesis: Intravenous midazolam (MDZ) area-under-the-curve (AUC) is used as a biomarker to phenotype hepatic cytochrome P450 (CYP) 3A activity. A recent study recommended a partial AUC from 2 to 4 hours with oral MDZ to predict metabolic clearance and thus CYP3A activity. We conducted a retrospective study to determine if a similar methodology is applicable

1704520: Table

	AUC_{0-2}	AUC_{0-4}	AUC_{0-6}
Regression Equation for predicted CL	-0.86^{*} [log(AUC_{0-2})] +2.58	-0.93^{*} [log(AUC_{0-4})] +2.79	-0.96^{*} [log(AUC_{0-6})] +2.88
r^2	0.94	0.96	0.97
Mean predicted CL (L/hr)	27.4	27.8	28.0
%MPE (±15%)	−1.80	−0.93	−0.62
%MAE (±15%)	13.01	10.52	8.67

with intravenous MDZ to predict systemic clearance (CL) and thus, hepatic CYP3A activity during baseline conditions.

Description of Methods and Materials: MDZ plasma concentrations were obtained from healthy subjects in seven published studies during baseline (n = 94) conditions. Observed MDZ CL and partial AUCs were obtained via non-compartmental analysis. Subject data were randomly divided into a training set (n = 30) and a validation set (n = 64). Linear regression analyses of dose-normalized, log-transformed partial AUCs were performed using training set data. A preset criterion for the derived regression equations was a $r^2 \geq 0.9$. Predicted CLs were then determined from validation set data. Back-transformed predicted CLs were compared to observed CLs. Relative bias and precision were assessed by percent mean prediction error (%MPE) and percent mean absolute error (%MAE), respectively.

Data and Results: Mean observed MDZ CL was 28.8 L/hr. Results of predicted CLs that met criteria are summarized in the Table.

Interpretation, Conclusion or Significance: In healthy adults, intravenous MDZ AUC_{0-2}, AUC_{0-4} and AUC_{0-6} were able to predict CL and thus baseline CYP3A activity.

1706528

Population Pharmacokinetics of Phenytoin in Mexican Adult Patients

Ossyneidee Gutierrez-Alvarez[1], Ismael Lares-Asseff[1], Luis Angel Ruano Calderon[2], Martha Sosa-Macias[1], Isaias Chairez-Hernandez[1], Fausto Zaruma-Torres[1], Jose Manuel Salas-Pacheco[3], Carlos Galaviz-Hernandez[1], Veronica Loera-Castañeda[1]

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Statement of Purpose, Innovation or Hypothesis: Many factors have been reported that contribute to the wide inter-patient variability of Phenytoin (Phe) disposition: polymorphisms in CYP2C9 and CYP2C19 genes, the body mass weight and the use of polytherapy. The purpose of this study was to develop a population pharmacokinetic model and to determine the covariates affecting the pharmacokinetics (PK) of Phe in Mexican adult patients.

Description of Methods and Materials: It was performed a population PK analysis that included 100 steady-state concentrations and associated dosage rates (mg/day) from 50 patients who were in treatment with oral Phe. The PK parameters (Vd, Vm, Km) were estimated by the non-linear mixed effect model using MONOLIX v4.2.0 a computer program designed for population pharmacokinetic analysis. It combines the SAEM (Stochastic Approximation Expectation/Maximization) algorithm, with a MCMC (Markov Chain Monte Carlo) procedure for maximum likelihood estimation in nonlinear mixed-effects models. We also illustrate how to use MONOLIX to build the covariate model using the Bayesian Information Criterion. The zero-order absorption rate in a one-compartment model, with Michaelis-Menten elimination kinetics, and an exponential error model were used to describe the concentration-time profile of Phe.

Data and Results: The maximum elimination rate (Vmax) was estimated to be 11.2 mg/kg/day, The Michaelis-Menten constant (Km) value was 0.327 mg/L. The volume of distribution (Vd) was 70.6 L. The interindividual variability of Vmax, Km, and Vd was estimated to be 0.00253%, 0.00574% and 0.0012% respectively. The Vd was significantly reduced in patients with polytherapy ($p < 0.01$).

Interpretation, Conclusion or Significance: The population pharmacokinetic parameters of phenytoin will be useful for designing dosage regimens in Mexican epileptic patients, whit the purpose of implementing personalized pharmacotherapy.

1708141

Population Pharmacokinetics of Cyclosporine in Mexican Pediatric Patients with Renal Transplants

Ismael Lares-Asseff[1], Samuel Saltzman-Girshevich[2], Fausto Zaruma-Torres[1], Ossyneidee Gutierrez-Alvarez[1], Gabriela Guillé-Pérez[3], Alejandra Toledo[3], Hugo Juárez-Olguín[3], José Trinidad Pérez-Urizar[4]

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Statement of Purpose, Innovation or Hypothesis: The purpose of the study was to determine the population pharmacokinetic (PPK) of cyclosporine (CsA) in children subjected to renal transplant.

Description of Methods and Materials: The study was conducted from 1948 retrospective drug monitoring data points were collected from 54 renal pediatric patients receiving CsA. For the structural model (PPK) the MONOLIX ® MLXTRANS program was used, the data were fitted using a two-compartment model with first order kinetics. The structural model was selected according to the best fit, according to criteria of-2Log likelihood, Akaike and Bayesian models.

Data and Results: To assess the effect of covariates on the response we carried out PPK correlation between parameters: Ka, Vd, K12, K21 and Ke with the variables of interest: age (months), sex, body mass index (BMI, kg/m2), current weight (kg), comprising postoperative days (POD), creatinine clearance (CrCl, mL/min), transplant rejection, and nutritional status (NS). Population values obtained were $Ka/F = 0.157 \pm 0.049$(h-1); $Vd/F = 0.323 \pm 0.064$ (Vd/F/70Kg) (L); $Ke/F = 0.145 \pm 0.03$ (h-1); $K12 = 7.58 \pm 23$ (h-1) and $K21 = 26.3 \pm 79$ (h-1). In assessing the influence of covariates of interest on the PPK of CsA, it was determined that the actual weight, the CrCl, the (RT) and (NS), showed significant correlation with Vd, and consequently with the CsACL, which determines interindividual variability. In order to correct for the influence of variables over response, we used the following equation: $Vd/F/70 = 0323\text{-}0508^{*}(CrCl\text{-}74)^{*}\text{-}0539(WT\text{-}37.5)\text{-}0562^{*}0566^{*}POD\text{-}NS\text{-}0456^{*}RT$ (L/70Kg).

Interpretation, Conclusion or Significance: In summary, the population pharmacokinetics model developed for CsA after administration in pediatric renal transplant patients was validated. The model obtained for CsA PPK can be useful for dose adjustment in pediatric Mexican patients, aimed at achieving therapeutic optimization of CsA.

1708416

Population Pharmacokinetics of Umeclidinium and Vilanterol in Patients With COPD

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Statement of Purpose, Innovation or Hypothesis: The long-acting muscarinic antagonist umeclidinium (UMEC) and the long-acting beta$_2$ agonist vilanterol (VI) are in development as monotherapies and as a combination therapy for chronic obstructive pulmonary disease (COPD). Population pharmacokinetic (POP-PK) analyses of UMEC and VI were performed using sparse plasma samples collected in two multicenter, randomized, double-blind, parallel-group Phase 3 efficacy and safety studies (DB2113361 and DB2113373) where UMEC (62.5 and 125 mcg) and VI (25 mcg) were administered as inhalation, alone or in combination for 24 weeks in patients with COPD.

Description of Methods and Materials: POP-PK models for UMEC and VI were developed using a standard stepwise approach in NONMEM® software. A likelihood-based approach was utilized to account for plasma samples with drug concentrations below the limit of quantification (~33%). A number of patient demographics and baseline characteristics were evaluated as covariates on UMEC and VI PK parameters. Goodness-of-fit plots, visual predictive checks, objective function value, and parameter precision were used for model selection.

Data and Results: A total of 8498 PK observations (N = 1635) contributed to UMEC and 8405 PK observations (N = 1637) contributed to VI POP-PK analyses. UMEC PK were adequately described by a two-compartment model with first-order absorption. Weight, age, and baseline creatinine clearance were significant covariates on apparent inhaled clearance and weight was a significant covariate on apparent volume of distribution. Analyses demonstrated that the effects of these covariates on UMEC PK were marginal and no dose adjustment was deemed necessary for UMEC based on these covariates. VI PK were best described by a two-compartment model with first-order absorption. Weight and age were significant covariates on apparent inhaled clearance. Effects of these covariates on VI PK were marginal and no dose adjustment was deemed necessary for VI based on these covariates. There was no PK interaction between UMEC and VI when administered as a combination.

Interpretation, Conclusion or Significance: The models adequately described the PK of UMEC and VI in patients with COPD. The analyses demonstrated that no dose adjustments in UMEC/VI, UMEC, or VI were warranted based on age, weight, and creatinine clearance in this patient population.

1708473

Comparison of Trough Dipeptidyl Peptidase-4 Inhibition in Patients With Type 2 Diabetes Treated with Saxagliptin, Sitagliptin and Vildagliptin

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Encore Presentation: *This abstract was submitted (but is not yet accepted) to European Association for the Study of Diabetes (EASD) 2013.*

Statement of Purpose, Innovation or Hypothesis: Saxagliptin (Saxa), sitagliptin (Sita), and vildagliptin (Vilda) are dipeptidyl peptidase-4 (DPP-4) inhibitors approved for use in treating type 2 diabetes. Here, we have assessed trough DPP-4 inhibition in a single cohort of patients treated with these agents.

Description of Methods and Materials: This was a randomized, placebo-controlled, open-label, five-period crossover study in which patients were treated for 5 days in each period. Eligible patients were 18–65 years of age and had A1C $\geq$6.5% and $\leq$10.0% when treatment-naïve or off prior AHA therapy for $\geq$6–12 weeks. Percent DPP-4 inhibition (%DPP-4i) was calculated for each treatment relative to the predose DPP-4 activity in each period. The primary endpoint (trough %DPP-4i 24 h after the morning dose on Day 5) was analyzed using a linear mixed-effects model with fixed-effects terms for treatment and period.

Data and Results: Mean (range) baseline A1C was 7.4% (6.4-9.0; N = 22). Least-squares (LS) mean trough %DPP-4i was 73.5%, 91.7%, 28.9%, 90.6%, and 3.5% after 5 mg Saxa q.d., 100 mg Sita q.d., 50 mg Vilda q.d., 50 mg Vilda b.i.d., and placebo q.d., respectively. In comparisons with Sita, LS-mean differences were 18.2% vs Saxa ($p < 0.001$; positive values favor Sita), 62.9% vs Vilda-q.d. ($p < 0.001$), 1.1% vs Vilda-b.i.d. ($p = 0.128$), and 87.8% vs placebo ($p < 0.001$). Since mean %DPP-4i was ~90% at 12 h postdose regardless of active treatment, these between-group comparisons primarily reflect differences in duration of action. Mean apparent t½ was 9.5 h for Saxa (14.7 h for its active metabolite 5OH-saxagliptin), 12.0 h for Sita, and 2.4–3.4 h for Vilda. Ten adverse events were reported overall, none serious. All were transient and mild or moderate in intensity.

Interpretation, Conclusion or Significance: Treatment with Sita provided DPP-4 inhibition significantly greater than either Saxa or Vilda once daily and similar to that provided by Vilda twice daily.

1708597

Pharmacokinetics of INXN-1001, an Activator Ligand to the Adenoviral Vector Ad-RTS-IL-12, in Healthy Human Subjects

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Statement of Purpose, Innovation or Hypothesis: A major obstacle for the development of effective immunotherapy is the ability of tumors to escape the immune system coupled with toxicity associated with systemic administration of immune-modulators. To overcome these challenges we have developed an adenoviral vector, Ad-RTS-IL-12, administered intratumorally under the control of the RheoSwitch Therapeutic System® (RTS®) platform. Expression of IL-12 is regulated by oral administration of a small molecule activator ligand, INXN-1001. Prior to introduction of Ad-RTS-IL-12 + INXN 1001 in patients, studies were conducted with INXN-1001 in healthy human subjects (HHS) to provide insight into dose-exposure relationship and effect of food on plasma pharmacokinetics.

Description of Methods and Materials: Pharmacokinetic data from three Phase I studies in HHS who received single or multiple daily oral doses of INXN-1001 ranging from 0.1 to 4 mg/kg or 200 mg were analyzed. Comparisons were made between the initial (Labrasol® oral slurry) and current (F-22 Hard Gelatin Capsule) formulations as well as between male and female subjects. The impact of food on single-dose pharmacokinetics of INXN-1001 was assessed in subjects following an overnight fast and after consumption of a high-fat or normal meal.

Data and Results: Pharmacokinetic data in HHS indicate that exposure to INXN-1001 increased with increase in dose after single- and multiple-dose administration. The increase in steady state INXN-1001 exposure was approximately dose proportional over the dose range of 1 to 3 mg/kg/day. No apparent formulation and gender-related difference in INXN-1001 pharmacokinetics was observed. Minimal or no plasma accumulation of INXN-1001 was observed after once-daily oral administration for up to 14 days, with steady state levels achieved within 8 days. Food consumption prior to INXN-1001 administration prolonged and enhanced absorption, resulting in significantly increased systemic exposure to INXN-1001, while having no impact on the elimination rate and extent of metabolism of INXN-1001.

Interpretation, Conclusion or Significance: INXN-1001 was well tolerated and exhibited an acceptable pharmacokinetic profile. INXN-1001 should be taken under fed conditions to ensure optimal absorption and sufficient systemic exposure for efficacy.

1708660

Effect of Food on the Relative Bioavailability of Two Oral Formulations of VX-661, an Investigational CFTR Corrector, in Healthy Adults

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Statement of Purpose, Innovation or Hypothesis: VX-661 is an investigational cystic fibrosis transmembrane conductance regulator (CFTR) corrector that increased F508del-CFTR protein activity *in vitro*. The aims of this study were to determine: 1) the relative bioavailability (BA) of VX-661 in tablet formulation compared with an oral solution; 2) the effect of food on systemic exposure for each formulation.

Description of Methods and Materials: This multi-part, first-in-human study examined the effects of VX-661 in healthy adults. We report results from Part B, a randomized, 4-way cross-over, BA and food effect study in 16 subjects. VX-661 pharmacokinetics was evaluated over 16 days following a single 100-mg dose of VX-661, either in solution or in tablet form, under fasting or fed (fat-containing meal) conditions.

Data and Results: The $AUC_{0\text{-}inf}$ values for the tablet and solution formulations were comparable under either the fed or fasted condition (Table). In the fed state, compared with the solution, the tablet formulation C_{max} was reduced by 12%. Administration with food did not significantly affect the $AUC_{0\text{-}inf}$ of either formulation. Food reduced C_{max} by approximately 30% for both formulations but did not affect T_{max} (median T_{max}: approximately 1 hour [solution] or 3 hours [tablet] in either fed/fasted state). The inter-subject variability of $AUC_{0\text{-}inf}$ and C_{max} was similar across groups.

Interpretation, Conclusion or Significance: The tablet formulation of VX-661 achieved similar exposure levels to those observed with solution, with slightly lower C_{max}. Administration of the tablet with food did not significantly alter drug exposure; however, the fed state was associated with a somewhat lower C_{max}. Together, these results suggest that the VX-661 tablet is an appropriate formulation for use in future clinical studies and may be administered with or without food.

1709290

Pharmacokinetic/Pharmacodynamic Analyses in Seraphin, a Randomized, Controlled Study of Macitentan in Patients With Pulmonary Arterial Hypertension

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Statement of Purpose, Innovation or Hypothesis: Macitentan is an orally active, novel dual endothelin $(ET)_A$ and ET_B receptor antagonist in clinical development for the treatment of pulmonary arterial hypertension (PAH). Macitentan significantly decreased the risk of morbidity and mortality compared to placebo in the SERAPHIN study (NCT00660179), a multicenter, double-blind, randomized, placebo-controlled, parallel group, event-driven Phase III study in patients with PAH. Pharmacokinetic/pharmacodynamic (PK/PD) relationships between macitentan steady-state trough plasma concentration after 3 mg and 10 mg o.d. dosing at month 6 ($n = 120$, PK/PD substudy) or end of treatment ($n = 393$) and efficacy and safety endpoints were investigated.

Description of Methods and Materials: Continuous parameters (hemodynamic parameters, exercise capacity measured by 6-minute walk distance [6MWD], and laboratory parameters) were analyzed using different structural models including E_{max} models. A logistic regression model was used to estimate the influence of macitentan concentration on the probability of experiencing an adverse event (AE) leading to study drug discontinuation.

Data and Results: Macitentan steady-state trough concentrations ranged from below limit of quantification to 801 ng/mL and arithmetic means showed a clear differentiation between the two doses (month 6: 92 ± 53 ng/mL and 291 ± 155 ng/mL, respectively; end of treatment: 76 ± 61 ng/mL and 208 ± 139 ng/mL, respectively). The PK/PD analysis indicated that higher macitentan concentrations were associated with a reduction in pulmonary vascular resistance, mean pulmonary artery pressure, and total pulmonary resistance and an increase in cardiac index and 6MWD. No relationship could be established between macitentan concentrations and mean right atrial pressure and mixed venous oxygen saturation. For safety parameters, macitentan concentrations were associated with changes of $<5\%$ in hematocrit, hemoglobin, and alanine/aspartate aminotransferase which were not clinically relevant. Macitentan concentrations were not associated with the probability of occurrence of an AE leading to study drug discontinuation.

Interpretation, Conclusion or Significance: In conclusion, no clear PK/PD relationship could be determined between macitentan trough concentration and safety parameters. For efficacy parameters, however, modeling showed that macitentan improves hemodynamic parameters and functional exercise capacity in a concentration-dependent manner in patients with PAH.

1708660: Table

Comparison	Subject Group	Parameter	GLSM ratio*	90% CI lower bound	90% CI upper bound
Tablet vs. Solution	Fasted (n = 16)	$AUC_{0\text{-}inf}$ C_{max}	0.977 0.791	0.934 0.708	1.02 0.883
Tablet vs. Solution	Fed (n = 16)	$AUC_{0\text{-}inf}$ C_{max}	1.04 0.879	0.989 0.786	1.09 0.984
Fed vs. Fasted	Tablet (n = 16)	$AUC_{0\text{-}inf}$ C_{max}	1.06 0.747	1.01 0.667	1.11 0.836
Fed vs. Fasted	Solution (n = 16)	$AUC_{0\text{-}inf}$ C_{max}	1.00 0.672	0.958 0.602	1.05 0.750

*GLSM: geometric least-squares mean

1709496

Prolonged-release Fampridine Pharmacokinetics (PK) in Healthy Caucasian, Japanese and Chinese Subjects

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Statement of Purpose, Innovation or Hypothesis: Prolonged-release fampridine (PR-F) tablets (dalfampridine extended release tablets in the US) are an approved treatment to improve walking in patients with MS. The objectives of this study were to characterize the PK and tolerability of a single 10 mg PR-F tablet in healthy Asia-Pacific and Caucasian populations and utilize results as a bridging study for conducting clinical trials in Asia-Pacific populations.

Description of Methods and Materials: This was a single-dose, open-label PK, safety, and tolerability study of one 10 mg PR-F tablet in healthy Caucasian, Japanese and Chinese volunteers. The dose was administered under fasted conditions. A total of 36 subjects (12 per ethnic group) completed the study. Blood and urine samples were collected at pre-specified times in the 24 hours after dosing. Plasma and urine samples were analyzed using a validated HPLC-MS method. PK parameters were determined by non-compartmental analysis. Safety and tolerability were assessed.

Data and Results: The PK parameters [(geometric mean (CV%)] following a single 10 mg PR-F tablet are listed below. No clinically significant findings were observed in vital signs, ECG and other laboratory tests. Adverse event (AE) profiles were comparable in three groups. No severe AE was observed in any subject.

Interpretation, Conclusion or Significance: A single dose 10 mg PR-F tablet was well tolerated in all subjects. The systemic exposure difference seen in Japanese and Chinese subjects compared to the Caucasian subjects was not clinically relevant. The lack of PK differences between Japanese and Caucasian subjects is also supported by a population PK analysis. No dose adjustment is suggested for Chinese or Japanese populations.

1709496: Table

PK parameters	Caucasians (N = 12)	Japanese (N = 12)	Chinese (N = 12)
Cmax (ng/mL)	18 (17)	23.7 (14)	20 (20)
AUCinf (h.ng/mL)	173.4 (21)	232.5 (28)	200.9 (23)
Median Tmax (h)	2	2	2
t1/2 (h)	4.4 (31)	4.5 (23)	4.6 (42)
CL/F (L/h)	57.7 (21)	43 (27)	49.8 (23)
CL/F/Kg (L/h/Kg)	0.8 (19)	0.7 (26)	0.8 (19)
CLr (L/h)	43.9 (21)	34.1 (16)	42.4 (16)

1709562

Novel Method to Calculate the Therapeutic Bioequivalence Between Two Famotidine Formulations by Gastric pH-metry

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Statement of Purpose, Innovation or Hypothesis: Many times a bioequivalence study done in a short number of volunteers is the only trial for approval a generic drug. Thus, is necessary that the test should be designed and performed in such a way that two important issues could be solved: are the results obtained not only scientifically but also technically valid enough?, and do these data reflect clearly that both compared formulations are bioequivalent and therefore interchangeable? Thereby, bioequivalenece studies that include therapeutic endpoints could be helpfull in order to respond such kind of questions. Aim: To assess the therapeutic bioequivalence of two pharmaceutical Famotidine formulations, in healthy volunteers by 24 hs gastric pH-metry

Description of Methods and Materials: Open-label, comparative, randomized, crossover study, single dose, with two treatment periods, isolated by a wash out phase. In 18 healthy volunteers 24 hs gastric pH-metry was performed. Day 0, the gastric sensor was placed in the volunteers, without medication. Sensor was extracted after 24 hs. Day 3, the gastric sensor was placed again, and ten minutes later one of randomized formulations was administrated: a) 1 chewable tablet of Famotidine (Ch) 10 mg or b) 1 sachet of Famotidine 10 mg, effervescent powder (Ef). Sensor was extracted after 24 hs. Day 10, the same procedure was done, but with the other pharmaceutical formulation. A curve with the pH-metry values obtained in different times was done. We take the percent time with pH under four to calculate the Area Under the Curve (AUC) of the first 12 hours (end point of comparison). A curve of the AUC1-12 for each formulation was done and the values of the AUC by a trapezoidal method was calculated. Finally, we obtained the quotient among the AUC of both formulations for determinate the therapeutic bioequivalence.

Data and Results: Ef: AUC1-6: 237,33; AUC1-12: 585,34. Ch: AUC1-6: 295,99; AUC1-12: 685,09. The AUC1-12 of the products were compared (Mann-Whitney, p = 0,2) and the calculation of the quotient among them was realized: AUC1-12: 0,85

Interpretation, Conclusion or Significance: The obtained values of the quotient among the AUC of both formulations, were included in range 80-125, which allows demonstrating the therapeutic bioequivalence between the formulations of Famotidine.

1709602

Development of a Minimal Physiologically-based Pharmacokinetic and Pharmacodynamic Model for Characterizing the Impact of Genetic and Demographic Factors on Clopidogrel Treatment Response in Healthy Adults

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Statement of Purpose, Innovation or Hypothesis: Plavix® (Clopidogrel, CLOP), a widely used antiplatelet agent, is an inactive prodrug that requires conversion to its active metabolite (CLOP-AM) by cytochrome P450 (CYP) enzymes, mainly by CYP2C19. Clinical evidence suggests that patients with deficient CYP2C19 activity are at an increased risk of ischemic events following the standard dosing regimen, which has led to a respective boxed warning from FDA. Polymorphisms in other enzymes, such as carboxylesterase (CES) 1, and demographic factors have also been shown to cause inter-individual variability in response to CLOP. The aim of this study was to develop a CLOP dosing algorithm to optimize CLOP treatment in patients receiving antiplatelet therapy.

Description of Methods and Materials: CLOP, CLOP-AM pharmacokinetic (PK) and pharmacodynamic (PD) data from the PAPI-1 and the NIH-FDA-PGx-B2B studies were included for PK/PD analysis. A minimal physiologically-based pharmacokinetic (PBPK) model was developed using a step-wise strategy in NONMEM (version 7.2) to characterize the bioactivation of CLOP to CLOP-AM in the liver. Model-predicted changes in plasma CLOP-AM concentration over time were then linked to the corresponding changes in platelet reactivity.

Data and Results: Our minimal PBPK/PD model was able to characterize the concentration-time profiles of CLOP and CLOP-AM as well as the corresponding platelet reactivity. While CES1 polymorphism impacted CLOP clearance, CYP2C19 status and BMI were identified as covariates for CLOP-AM formation. In addition, age was identified as a covariate for baseline platelet reactivity.

Interpretation, Conclusion or Significance: A minimal PBPK/PD model was developed that allows to characterizing and predicting interindividual differences in the CLOP dose-concentration-platelet reactivity relationship due to polymorphisms in CYP2C19 and CES1 as well as BMI and age in healthy adults. This model will be used to develop a bedside-ready dosing algorithm to optimize anti-platelet therapy on a patient-by-patient basis.

1709861

Comparison of Pharmacokinetics (PK) and CD20$^+$ B-cell Depletion (PD) in Mild Rheumatoid Arthritis (RA) and Systemic Lupus Erythematosus (SLE) Patients Following Administration of an Anti-CD20 Protein Therapeutic

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Statement of Purpose, Innovation or Hypothesis: To compare PK, CD20$^+$ B cell kinetics and their relationship between mild RA and SLE patients following SBI-087 administration in Phase 1 studies.

Description of Methods and Materials: SBI-087 is a monospecific molecule, built on the ADAPTIR™ (modular protein technology) platform, directed against CD20$^+$, a transmembrane lineage-restricted protein present on B cells. SBI-087 concentrations and CD19$^+$ (surrogate for CD20$^+$) B cell counts from above patient populations were compared. For this comparison, serum samples following subcutaneous administration in 32 mild RA and 24 mild SLE patients up to 84 days post dose were considered. Non-compartmental parameters derived from the PK and PD data were compared for above patient populations. Using exploratory datasets, a mixed-effects cell kill sequential model was developed using NONMEM. The optimal PK model was a two-compartment model with a zero and first order absorption and linear elimination from central compartment. The PD model included a zero-order B cell formation rate, a first-order cell death rate, a second order cell kill process and B cell distribution parameters. Parameters from the population PK/PD model were compared between the two populations.

Data and Results: SBI-087 PK was similar to other large molecules with slow clearance (CL/F) and small volume of distribution (Vz/F). Non-compartmental parameters were similar between the two populations, CL/F in RA: 0.045 to 0.077 L/hr vs. SLE: 0.046 to 0.105 L/hr; Vz/F in RA: 14.3 to 22.7 L vs. SLE: 19.9 to 32.1 L. The rate and extent of B cell depletion was more profound and less variable in RA than SLE. Above trend was also reflected in the population PK/PD model parameters.

Interpretation, Conclusion or Significance: While SBI-087 PK properties were similar in mild RA and SLE patient populations, the rate, extent and duration of CD19$^+$ B cell depletion was more profound in RA than in SLE patients. These findings suggest the need to consider exploration of different dosing regimens in future RA and SLE studies.

1710198

Pharmacokinetics and Pharmacodynamics of Ustekinumab in Two Phase 3 Studies in Patients With Active Psoriatic Arthritis

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Statement of Purpose, Innovation or Hypothesis: To assess pharmacokinetics (PK) and exposure-response of ustekinumab in psoriatic arthritis (PsA) patients.

Description of Methods and Materials: In 2 Phase 3 studies (PSUMMIT 1 [n = 615, all naïve to anti-TNF agents] and PSUMMIT 2 [n = 312, 180/312 with prior exposure to anti-TNF agents]), adults with PsA were randomized to receive ustekinumab 45 mg, 90 mg, or placebo at Weeks 0, 4, and q12wks thereafter. At Week 16, patients with <5% improvement in tender/swollen joint counts entered blinded early-escape (placebo→45 mg; 45 mg→90 mg; 90 mg→90 mg). Stable methotrexate (MTX) was allowed. Blood samples were collected at selected visits and serum ustekinumab-concentrations were measured using a validated immunoassay. Ustekinumab-concentrations were statistically summarized with an additional confirmatory population PK analysis (NONMEM®). The relationships between ustekinumab-concentrations and selected efficacy-endpoints were explored graphically.

Data and Results: Dose-proportionality in ustekinumab-concentrations was observed. Steady-state was achieved at Week 28 and trough ustekinumab-concentrations maintained at steady-state through Week 52 with no evidence of accumulation in ustekinumab-concentrations over time. Among demographic factors, baseline patient physical/biochemical characteristics, medical/medication history, and concomitant medications evaluated, only body weight and positive antibody-to-ustekinumab status were confirmed to be important covariates affecting the CL/F, thus the systemic-exposure to ustekinumab. No other factors evaluated (eg, concomitant MTX, NSAIDs, oral corticosteroids, or prior exposure to anti-TNF agents) appeared to have clinical relevant impacts on the CL/F. Patients >100 kg had generally lower systemic-exposure compared with patients ≤100 kg. Notably, systemic-exposure in patients >100 kg treated with 90 mg was generally comparable to those in patients ≤100 kg treated with 45 mg. The proportions of patients who achieved ACR 20, ACR 50, and/or PASI 75 responses at Week 52 were generally higher in patients with higher trough ustekinumab-concentrations.

Interpretation, Conclusion or Significance: The PK and exposure-response findings are consistent with those from previous Phase 3 studies in patients with moderate-to-severe plaque psoriasis. While both 45 mg and 90 mg doses are efficacious, the 90 mg dose may provide greater benefits for patients with heavier weight (>100 kg).

1710219

Population Pharmacokinetic-Pharmacodynamic Modeling of Caffeine Using Visual Analogue Scales

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Statement of Purpose, Innovation or Hypothesis: To develop a population pharmacokinetic-pharmacodynamic (PK-PD) model for

orally administered caffeine in healthy volunteers using visual analogue scale (VAS) responses

Description of Methods and Materials: Twelve healthy, moderate caffeine consuming volunteers were recruited for a three-period cross-over study which assessed three beverages, each containing 100mg of caffeine. Pharmacokinetic samples were collected at 0–8 hours. Caffeine pharmacodynamics were evaluated using a 100 mm VAS at 0–4 hours which assessed the following: lethargic-vigorous,muddled-clear-headed,tired-energetic,unimaginative-imaginative,listless-full of go, and inefficient-efficient. PK-PD modeling was conducted with NONMEM 7.2. Simultaneous and sequential modeling of plasma caffeine concentration and VAS responses were attempted. One and two-compartment models were tested as structural pharmacokinetic models while linear, Emax, sigmoidal Emax and effect compartment models were tested for pharmacodynamics. Approximately 45% of subject visits had measurable pre-dose concentrations due either to non-compliance with the protocol or the relatively short 12-hour caffeine fast. For these visits, a method (Exogenous example, NONMEM guide) to account for unknown dosing history was implemented to explain pre-dose concentrations. Final model selection was based on examination of parameter estimate precision, diagnostic plots, and visual predictive check (VPC) plots.

Data and Results: A one-compartment open model with first-order absorption and elimination best described the pharmacokinetics of caffeine. Typical values of absorption rate constant, elimination rate constant and volume of distribution were estimated as 1.76hr-1,0.16hr-1 and 46.3L, similar to previous reports. Sequential PK-PD modeling was successful and an effect compartment model with linear slope and baseline parameters described all pharmacodynamic variables. The estimated baseline and slope for each pharmacodynamic variable were >30 mm and >1.4 respectively indicating a baseline response and responsiveness to caffeine. Diagnostic plots showed no major bias and parameter confidence intervals did not include zero. VPC plots showed agreement between observations and predictions.

Interpretation, Conclusion or Significance: A population PK-PD model was developed for caffeine in healthy volunteers which adequately described the concentration-time profile and associated VAS responses.

1710232

Immunogenicity and Clinical Relevance of Ustekinumab in Two Phase 3 Studies in Patients With Active Psoriatic Arthritis

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Statement of Purpose, Innovation or Hypothesis: To assess the immunogenicity of ustekinumab (anti-drug antibodies [ADA]) and its clinical relevance in patients with psoriatic arthritis (PsA).

Description of Methods and Materials: In two Phase-3 studies (PSUMMIT-1 [n = 615, all naïve to anti-TNFα agents] and PSUMMIT-2 [n = 312, 180/312 with prior exposure to anti-TNFα agents]), adult patients with PsA were randomized to receive ustekinumab 45 mg, 90 mg, or placebo at Weeks 0, 4, and q12wks thereafter. At Week-16, patients with <5% improvement in tender/swollen joint counts entered blinded early-escape (placebo→45 mg; 45 mg→90 mg; 90 mg→90 mg). Patients randomized to placebo crossed-over to 45 mg at Week-24. Stable methotrexate (MTX) was permitted. Serum samples were collected up to Week-60 and ADA were detected using a sensitive and drug-tolerant immunoassay. The incidence of ADA was summarized. The effects of ADA on pharmacokinetics, efficacy, and injection-site-reactions (ISRs) were explored.

Data and Results: The incidence of ADA was low (overall 7.8%) and generally comparable between the 45 mg and 90 mg groups (8.9% vs 7.7%). The incidence was lower in patients receiving MTX compared with patients not receiving MTX (4.6% vs 10.8%; not associated with efficacy); higher in patients with prior exposure to anti-TNFα agents compared with anti-TNFα naïve patients (12.3% vs 6.8%); higher in patients >100 kg compared with patients ≤100 kg (14.5% vs 5.5%); and higher in patients with unquantifiable trough drug-concentrations compared with patients with quantifiable trough drug-concentrations (21.8% vs 2.6%). The majority (64.7%) of ADA were able to neutralize the bioactivity of ustekinumab *in vitro*. ADA-positive patients tended to have higher clearance (CL/F) and lower serum ustekinumab concentrations, and exhibited generally lower efficacy in American College of Rheumatology (ACR)-20 and ACR-50 responses. However, ADA-positivity did not preclude an efficacy response. ADA-positivity was not associated with ISRs: 4/288 ustekinumab-injections in 2/68 (2.9%) ADA-positive subjects and 14/3458 ustekinumab-injections in 23/802 (2.9%) ADA-negative subjects had ISRs (all mild).

Interpretation, Conclusion or Significance: The incidence of ADA was low and generally consistent with previous Phase-3 studies in patients with psoriasis. Clinical monitoring of ADA is not warranted.

1710289

Pharmacokinetics of the IFN-free Combination of BI 207127 and Faldaprevir Plus Ribavirin in Treatment-naïve Patients With HCV GT1: Results From SOUND-C1

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Statement of Purpose, Innovation or Hypothesis: SOUND-C1 (Phase Ib) investigated the IFN-free combination of faldaprevir (HCV NS3/4A protease inhibitor), BI207127 (non-nucleoside NS5B inhibitor), and ribavirin (RBV) in treatment-naïve patients with HCV GT1; rapid virologic response rates were up to 100% (BI 207127 600 mg TID group) and treatment was well tolerated.

Description of Methods and Materials: This open-label randomized study had two 4-week treatment arms: faldaprevir 120 mg QD (FDV_{QD}) + BI 207127 400 mg TID (7127-400_{TID}) + RBV and FDV_{QD} + BI 207127 600 mg TID (7127-600_{TID}) + RBV. Blood samples were taken on Day 10 for PK analysis of each drug pre- and post-dose under fed conditions. Data from previous co-administration studies of BI 207127 and faldaprevir (when no drug-drug interaction was found) were used for comparison.

Data and Results: Fifteen patients were randomized to Group 1 (7127-400_{TID}) and 17 patients to Group 2 (7127-600_{TID}). The increase in BI 207127 C_{max} and AUC for 600 mg vs 400 mg was slightly more than dose-proportional, but variability was high. Faldaprevir C_{min} levels were higher with 7127-600_{TID} than 7127-400_{TID}. The PK of RBV were comparable in both groups. Plasma concentrations of all drugs were higher in females than males. Combination of BI 207127 with faldaprevir resulted in 3-8-times higher BI 207127 C_{min} concentrations vs BI 207127 alone. Combination also increased the multiple-dose C_{max} and AUC of faldaprevir (1.3-2-fold) vs faldaprevir alone. However, increases were transient and C_{min} concentrations of both drugs began decline after ~2W.

Interpretation, Conclusion or Significance: As BI 207127 exposure increased in the presence of faldaprevir, investigation of BI 207127 BID dosing is warranted when combined with faldaprevir. The

PK profile of faldaprevir, alone and combined with BI 207127, continues to support 120 mg QD dosing. These results indicate that each drug affects the clearance of the other; the increased C_{min} levels of both drugs may therefore improve the regimens efficacy profile. The mechanisms underlying the interaction are under investigation.

1710307

Retrospective Validation Using PK/PD Modeling of ECG Data Derived From a Single Ascending Dose Study in Accordance With the Principles of the ICH E14 Guideline Utilizing the Effects of a Meal to Establish Assay Sensitivity

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Statement of Purpose, Innovation or Hypothesis: A vast proportion of Thorough QT (TQT) studies use moxifloxacin (400 mg) as a positive treatment arm to assure assay sensitivity as per ICH E14 guidelines. However, moxifloxacin produces a QTc change greater than the 5 msec threshold proposed by the guidelines. Recently we have shown that food produces QTc shortening effect (Taubel et al., 2012) correlated closely with the release of C peptide and blood glucose concentrations (Taubel et al., 2013). In this double blind placebo controlled, 4-way cross-over study Phase I study, 32 healthy male and female subjects were randomised to receive single and multiple doses of S1RA at three ascending dose levels and placebo. A retrospective validation was performed using PK-PD modelling with ECG data derived from a single ascending dose study in accordance with ICH E14 guidelines utilising a meal to establish assay sensitivity.

Description of Methods and Materials: To investigate this, the primary analysis is based on QTcF. The effect of IMP concentration on the change in QTc from baseline are assessed using a mixed effect model with sequence, period, and sex as fixed effects, concentration as the study variable, and subject as random effect. Two-sided 95% confidence intervals for the concentration effect are derived. A linear concentration response model with change from baseline of QTcF as dependent variable and plasma concentrations of the sigma-1 receptor antagonist are used. In a model not based on change from baseline, factors for time and day are included allowing separating the estimates of food and drug induced effects.

Data and Results: The study evaluation showed that there was no discernible effect of the S1RA on the QTc in the time course and pk-pd analysis. Yet a positive control was not used in this study and therefore this analysis was performed to provide a measure of assay sensitivity using a meal as positive control.

Interpretation, Conclusion or Significance: This work serves to show that the value of Intensive QT (IQT) studies is significantly enhanced by the analysis of food effects allowing the benchmarking of the ECG data against a well defined and reproducible physiological probe for assay sensitivity.

1710346

Pharmacokinetics and Bioavailability Assessment of an Anti-oxLDL Monoclonal Antibody, MLDL1278A, in Healthy Volunteers

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Statement of Purpose, Innovation or Hypothesis: MLDL1278A (or BI-204) is a fully human recombinant monoclonal antibody directed against the oxidized low-density lipoprotein (oxLDL) epitope malon-dialdehyde-modified human ApoB-100. A previous phase I study showed a notable difference in bioavailability (F) for subjects receiving an intravenous (IV) infusion 2–3 months prior to the subcutaneous (SC) dose of MLDL1278A vs. those receiving only SC doses of MLDL1278A. This study is to estimate the SC bioavailability; explore the effect of a prior IV dose on SC bioavailability; characterize pharmacokinetics (PK), safety, tolerability and immunogenicity of MLDL1278A.

Description of Methods and Materials: Two parallel cohorts of healthy subjects were enrolled. Subjects in Cohort A ($n = 12$) participated in two study periods. In Period 1, Cohort A subjects received a single IV infusion of 360 mg MLDL1278A. Following a washout period of at least 70 days (up to 91 days), these subjects then received a single SC dose of 360 mg MLDL1278A (Period 2). Subjects enrolled in the parallel cohort, Cohort B ($n = 10$), only participated in one period. Each Cohort B subject received a single SC dose of 360 mg MLDL1278A with 70 days followed up. Serum samples were collected at multiple times for PK and anti-therapeutic antibodies (ATA) assessments.

Data and Results: MLDL1278A was generally well tolerated when administered by IV infusion or SC injection. Following a single SC dose of 360 mg, MLDL1278A was slowly absorbed with a median Tmax of 4 days. The bioavailability averaged at 56% (90%CI: 51%, 62%) and 47% (90%CI: 40%, 55%) for cohort A and B subjects, respectively. The systemic clearance, steady state volume of distribution and elimination half-life averaged 906 mL/day, 15.2 L, 20 days, respectively, after a single IV dose. None of the MLDL1278A treated subjects tested positive for ATA.

Interpretation, Conclusion or Significance: MLDL1278A was well tolerated with no detectable ATA response after 360 mg IV, SC, or IV followed by SC administration. SC Bioavailability averaged 47–56%. The impact of a prior IV dose on bioavailability of the subsequent SC dose is minimal.

1710421

Pharmacokinetics and Pharmacodynamics of Ranolazine in Patients With an Implantable Cardioverter Defibrillator Receiving Amiodarone

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Statement of Purpose, Innovation or Hypothesis: To evaluate the pharmacokinetics (PK) and pharmacodynamics (PD) of ranolazine (RAN) in patients with an implantable cardioverter defibrillator receiving stable amiodarone (AMIO), defined as the same dose for at least 60-days.

Description of Methods and Materials: Eleven adult patients [mean ± SD age = 64 ± 18; creatinine clearance (CrCL): 60 ± 26 ml/min (range: 35–120 ml/min)] were given RAN (extended-release) 500mg twice daily for three days. In addition to baseline, on day 3, blood samples and 12-lead electrocardiograms were collected at 0, 2, 4, 6, 8, and 12 hours. Serum RAN concentrations were determined by liquid chromatography-tandem mass spectrometry. Population PK was conducted by non-parametric adaptive grid (BigNPAG) with adaptive gamma, employing a 2-compartmental model (absorption and plasma) with mixed non-linear (Michaelis-Menten) and linear elimination (made

proportional to CrCL). The observed RAN concentration and its effect on delta-QTc at that time point were fit to linear model to describe the PD relationship (SigmaPlot, version 12.0).

Data and Results: The population estimates of KM, Vd, Ka, and Tlag were 3238 ng/mL, 162.2 L, 0.247h-1, and 1.61 h, respectively. Total RAN clearance was 30.2 ± 20.5 L/hr, and 50 ± 17% of clearance was by nonlinear metabolism in this population with remaining clearance predicted by CrCL. A significant positive association [f = 21.9 + 0.0286 * x (p = 0.0133), where f is the change in patients QTc interval, and x is the concentration of ranolazine in ng/mL] between increasing RAN serum concentrations and increasing QTc interval was observed (p = 0.0133).

Interpretation, Conclusion or Significance: When administered concomitantly with AMIO, our observed RAN PK is in line with the observations of RAN PK alone in healthy volunteers, based on historical cross-study comparison. A positive relationship between plasma RAN and QTc prolongation was observed, although greater than seen in previous RAN publications. The results are limited by the small sample and observation numbers as well as lack of double-delta QTc analysis.

1710441

Comparative Bioavailability of Two Oral Formulations of Phentermine in Healthy Volunteers

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Statement of Purpose, Innovation or Hypothesis: Phentermine is an anorexygenic drug used as adjuvant for weight loss treatment. Currently, several branches of this drug are available in Mexico, however, no information about its pharmacokinetics is available. The purpose of this study was to compare the bioavailability of two phentermine formulations in healthy volunteers.

Description of Methods and Materials: Twenty-six subjects received the two formulations tested, IFA Acxion® (capsule with 30 mg of phentermine, formulation A) and Terfamex® (capsule with 37.5 mg of phentermine, formulation B) after at least 10 h fasting under a cross-over design. Blood samples were obtained at selected times during a 96 h period and plasma was obtained and stored frozen at −80°C until analyzed by HPLC coupled to MS/MS detection.

Data and Results: Pharmacokinetic parameters (mean ± s.e.m.) obtained were: Cmax 109.87 ± 4.97 and 135.25 ± 7.21 ng/ml, tmax 3.50 ± 0.26 and 4.46 ± 0.86 h, AUClast 3171.70 ± 186.14 and 3817.99 ± 208.46 ng.h/ml, for formulations A and B, respectively. Since the administered dose was different, data were normalized, log transfored and compared by analysis of variance followed by determination of ratio and 90% confidence limits of the pharmacokinetic parameters.

Interpretation, Conclusion or Significance: Since 90% confidence limits of Cmax and AUC ratios were included in the limits of acceptance for bioequivalence (80–125%), it is concluded that the formulations of phentermine tested are bioequivalent.

1710444

Population PK Analysis of Canakinumab in Patients With Schnitzler's Syndrome

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Statement of Purpose, Innovation or Hypothesis: Canakinumab is a high-affinity fully human monoclonal antibody that neutralizes the activity of a pro-inflammatory cytokine interleukin-1β (IL-1β). Schnitzler's syndrome is a rare chronic disabling autoinflammatory disorder. It is believed that IL-1β plays a pivotal role in the pathophysiology of this debilitating disease. A clinical study was conducted to assess efficacy, safety, tolerability, pharmacokinetics (PK) and pharmacodynamics (PD) of canakinumab. In this research work, PK/PD and population PK analysis was performed with the data in patients with Schnitzler's syndrome and simulations were performed to predict the concentrations at time of flare.

Description of Methods and Materials: In this open-label, single-arm 9-month trial, patients received 150 mg canakinumab subcutaneous injections every 4 weeks for 6 months and were followed for up to 3 months or until relapse. In addition to clinical evaluation, blood samples were collected at 5 times points during first month and pre-dose thereafter in the patients receiving repeat dose. Serum canakinumab and total IL-1β concentrations were measured using a validated ELISA method. PK analysis was performed by a population PK model implemented using NONMEM. The objective function values (OFV) and visual predictive check (VPC) were used as criteria for PK model selection and validation. Concentrations at the time of flare were determined and simulations for different dosing scenario were performed to achieve drug levels above the flare concentration in most patients.

Data and Results: Complete or clinical remission was achieved at Day 14 in all patients. Relapse after the last canakinumab dose occurred at least after 1.5 months. Following administration of canakinumab, an increase in total IL-1β was observed indicating binding with IL-1β. Preliminary population analysis of PK data suggests that a two-compartmental model with linear clearance adequately captures individual serum concentration-time profiles of canakinumab in most subjects. The apparent serum clearance (CL/F) value was estimated to be 0.279 L/d, which is comparable to the CL/F of 0.243 L/d in CAPS and 0.334 L/d in gouty arthritis patients.

Interpretation, Conclusion or Significance: Mean systemic clearance and other PK parameters were comparable to that of CAPS and gouty arthritis patients. The pharmacokinetics of canakinumab in patients with Schnitzler's syndrome is consistent with those observed in CAPS and gouty arthritis patients.

1710448

Evaluation of the Possible Pharmacokinetic Interaction Between Domperidone and Magaldrate

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Statement of Purpose, Innovation or Hypothesis: Domperidone is a dopaminergic antagonist that is used to regulate gastric motility, whereas, magaldrate is local acting antacid agent. Recently, a new formulation containing both compounds was developed to be used in the treatment of gastric reflux, however, it is important to establish if there is pharmacokinetic interaction between these compounds, since, it has been described that domperidone absorption may be reduced when is coadministered with antacids.

Description of Methods and Materials: Twenty-six healthy volunteers were included in the study. All subjects received two formulations: domperidone 10 mg suspension (formulation A) or domperidone-magaldrate (10/800 mg) suspension (formulation B)

after at least 10 h fasted under a cross-over design. Blood samples were collected during a 48 h period and plasma was obtained and stored frozen at −80°C until analyzed by HPLC coupled to fluorescence detection.

Data and Results: Pharmacokinetic parameter obtained were: Cmax 6.449 ± 1.011 and 5.740 ± 0.696 ng/ml, tmax 1.488 ± 0.241 and 1.303 ± 0.227 h, ABC48h 16.278 ± 2.690 and 22.681 ± 7.091 ng.h/ml, ABCinf 34.477 ± 8.096 and 29.532 ± 8.822, and t1/2 4.588 ± 1.290 and 6.676 ± 2.832 h for formulations A and B, respectively. No statistically significant difference in any parameter was observed

Interpretation, Conclusion or Significance: Results seem to indicate that magaldrate does not affect the oral pharmacokinetics of domperidone and therefore, they can be administered in a fixed dose combination.

1710675

Continuous Infusion of Mycophenolate Mofetil for Acute Graft-Versus-Host-Disease Prophylaxis Appears to Be Safe and Effective in Pediatric Bone Marrow Transplant Patients

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Statement of Purpose, Innovation or Hypothesis: Graft versus host disease (GVHD) is a common and fatal complication following hematopoietic stem cell transplantations (HSCT). Mycophenolate mofetil (MMF), a prodrug of the active form mycophenolic acid (MPA) is widely used in combination with cyclosporine as a maintenance immunosuppressive agent to prevent GVHD. AUC < 60 μg*hr/ml has been associated with higher rates of acute GVHD in adult HSCT patients. Most MPA dosing regimens and pharmacokinetic (PK) parameters have been established in solid organ transplant recipients and none of these strategies have been successful in reaching targeted AUC concentrations in pediatric HSCT patients. We hypothesize that a PK based AUC-targeting dosing strategy using continuous infusion (CI) MPA will reduce acute GVHD rates. The objective of this study was to evaluate the safety and feasibility of an AUC-based MMF dosing regimen for GVHD prophylaxis in pediatric HSCT patients.

Description of Methods and Materials: Pediatric patients (n = 13) undergoing HSCT were given MMF and cyclosporine based GVHD prophylaxis regimen. MMF was started at a dose of 15 mg/kg IV short infusion given over 2 hrs every 8 hours from the day of transplantation. MMF IV short infusion was converted to MMF IV CI targeting a 1.7–3.3 μg/ml steady-state concentration (Css). CI was then converted to oral dosing (Q8hrs) targeting a 1–3.5 μg/ml trough concentration (Ctrough). MPA concentrations were measured by a validated HPLC-MS-MS methodology.

Data and Results: This PK study showed significantly lower half-life (2–3 hours) and high oral and intravenous drug clearance (10 L/hr) in pediatric HSCT recipients. CI MMF was shown to be well-tolerated. No infusion related adverse events were seen and targeted steady-state levels were achieved with CI of MMF. CI of MMF appears to be safe and effective in pediatric HSCT patients.

Interpretation, Conclusion or Significance: CI MMF was shown to be well-tolerated. No infusion related adverse events were seen and targeted steady-state levels were achieved with CI of MMF. CI of MMF appears to be safe and effective in pediatric HSCT patients.

1710713

Impact of Female Hormones on Regulation of Hepatic Drug Metabolism

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Statement of Purpose, Innovation or Hypothesis: Pregnancy related hormones modulate the expression and activity of various drug metabolizing enzymes in humans. Our goal therefore is to evaluate the effect of various female hormones on the expression and activity of major cytochrome P450 enzymes and UGT's in human primary hepatocytes.

Description of Methods and Materials: Two primary human hepatocytes from female donors were treated with vehicle or low [progesterone (2 μM), estradiol (0.3 μM), estriol (0.8 μM), estrone (0.2 μM), 17-α hydroxyprogestrone (0.1 μM) and human growth hormone (0.005 μM)] and 10-fold high concentrations of hormone combination for 72 hours. The media were replaced with a validated CYP cocktail of phenacetin (CYP1A2), testosterone (CYP3A4/5), diclofenac (CYP2C9), S-mephenytoin (CYP2C19) and dextromethorphan (CYP2D6). Liquid chromatography-tandem mass spectrometry (LC-MS/MS) was used for assaying the respective metabolite concentrations of the above substrates and the mRNA expression of the major CYPs was examined by using qRT-PCR.

Data and Results: Our results showed that low and high concentrations of hormones enhanced the activity of CYP1A2 (1.3 and 2.3 fold respectively). However, the activity of other CYP450 enzymes (CYP2C9 CYP2D6, CYP3A4, and CYP2C19) did not change. Our data also showed that low and high concentrations of hormones increased the mRNA expression of CYP1A2 (1.6 fold), CYP2D6 (2 fold), CYP3A4 (1.3 and 2.6 fold respectively), but did not change the expression of CYP2C9 or CYP2C19.

Interpretation, Conclusion or Significance: Our observations suggest that additional mechanisms might be responsible for the observed increase in *in vivo* effect of pregnancy on certain CYP enzymes.

1711109

Pharmacokinetics of Propofol in Pediatric Obese Population

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Statement of Purpose, Innovation or Hypothesis: Propofol is widely used to induce anesthesia in surgery. Current propofol dosing is calculated based on total body weight. However, lipophilic drugs as propofol may extensively distribute into adipose tissues in obese patients. The pharmacokinetics (PK) of propofol in obese individuals may be different from those in non-obese counterparts. The goal of this study is to determine the impact of obesity in propofol PK in pediatric population.

Description of Methods and Materials: Patients between ages 3 to 12 years presenting for ambulatory surgery at Texas Children's Hospital were included in the study. BMI between 25th and 84th percentile were categorized as non-obese group. Patients of BMI > 95 percentile were

1711109: Table

Group	N	Body Weight (Kg)	BMI percentile	CL (L/hr/kg)	CL2 (L/hr/kg)	K21 (hr-1)	Beta_HL (hr)	MRT (hr)
Obese	5	51.6	97	3501	4810	0.30	8.62	6.53
Normal	3	39.6	55	5321	18632	0.89	4.47	2.94

obese. Propofol was administrated by IV bolus 3 mg/kg. Blood (0.5 ml) were collected at 0, 2, 15, 30 min, 4, 8, 12, and 24 hr after dosing. Propofol was extracted from plasma by acetonitrile and analyzed by a validated LC/MS/MS assay. Plasma profiles were constructed and PK parameters were derived by WinNonlin.

Data and Results: The assay linearity of 5 – 6400 ng/ml was established with $R2 > 0.99$. PK parameters were generated by WinNonlin. We observed slower CL and CL2, decreased K21 and longer beta half life and MRT in obese patients.

Interpretation, Conclusion or Significance: Slower CL2 in the obese indicates less propofol returns to the central compartment and more remains in the peripheral compartment. The slower CL2 may explain the observation of smaller ED95 in obese (2 mg/kg) to initiate unconsciousness than in lean group (3.2 mg/kg). Longer beta half life and MRT may account for the retention of propfol in the higher fat tissue content of obese patients.

1712384

Pharmacodynamic Approach to Generic Immunosuppressive Drugs

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Encore Presentation: *The Second Indiana Clinical and Translational Sciences Institute (CTSI) Symposium on Disease and Therapeutic Response Modeling - November 13, 2012.*

Statement of Purpose, Innovation or Hypothesis: Simulate the differences between pharmacokinetic and pharmacodynamic bioequivalence of tacrolimus and the impact into interchangeability

Description of Methods and Materials: With average pharmacokinetic data of tacrolimus in patients were simulated 48 pharmacokinetic profiles. A first group of 24 pharmacokinetic profiles was generated; their concentrations were within a range of variation of 20%, to second group of 24 patients their variability was within 90% of concentration, variation similar to that shown in patients. Pharmacodynamic tacrolimus parameters to Emax model, effective concentration to 50% (EC50%), maximum effect (Emax) and Hill's number (h) were obtained from pharmacodynamic data published from Millan et al. 2003. Applying the model of Emax was calculated to each pharmacokinetic profile the relation PK-PD. Ones calculated the PK/PD relationship were applied the accepted bioequivalence criteria to pharmacokinetic profiles and effect in to the time. The simulations were made in conventional data sheet (Microsoft® Excel 2011 for Mac Version 14.1.2).

Data and Results: Bioequivalence simulation of tacrolimus shows that is possible to a formulation can meet the criteria of bioequivalence, however, it not be pharmacodynamic.

Interpretation, Conclusion or Significance: The fact that tacrolimus could show pharmacokinetic bioequivalence criteria right not mean that the generic formulation reflex the same effect. Drugs witch pharmacodynamic profile shows a steep slope could reflex a probable difference at pharmacodynamic result. Small changes at concentration reflex great changes at the effect.

1716464

Sirukumab Pharmacokinetics Following Multiple Subcutaneous Administrations in Patients With Rheumatoid Arthritis Despite Methotrexate Therapy

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Statement of Purpose, Innovation or Hypothesis: The objectives of this Phase 2 study included proof-of-concept (Part A) and dose-finding of sirukumab, a human monoclonal antibody targeting interleukin (IL)-6, for the treatment of active rheumatoid arthritis (RA) (Part B).

Description of Methods and Materials: In Part A, 36 RA patients were randomized (1:1) to placebo or 100 mg sirukumab every two weeks (q2w) through 10 weeks and crossed over to the other treatment through week 22. In Part B, 151 RA patients were randomized (1:1:1:1:1) to placebo q2w (crossover to sirukumab 100 mg q2w at week 12), sirukumab 100 mg q2w, 100, 50 or 25 mg every four weeks (q4w) through week 24. Serum samples were collected and analyzed using a validated electrochemiluminescent immunoassay. Sirukumab PK parameters were derived using non-compartmental analysis.

Data and Results: The mean (SD) sirukumab PK parameters are summarized in Table 1. The mean C_{max} and $AUC_{0\text{-}28d}$ increased in an approximately dose-proportional manner following SC administration of sirukumab 25 -100 mg q4w. Serum sirukumab concentrations achieved steady state by week 12, with mean trough concentrations of 0.99, 1.79, 3.10, and 11.63 μg/mL for the sirukumab 25, 50, 100 mg q4w, and 100 mg q2w groups, respectively. Only 2 patients (2/173,1.2%) tested positive for antibodies to sirukumab.

Interpretation, Conclusion or Significance: Sirukumab exhibited linear PK in the dose range of 25–100 mg following multiple SC

1712384: Bioequivalence data

	Reference			Test		
	AUC Pk	Cmax	AUC Eff	AUC Pk	Cmax	AUC Eff
Average	295.3	36.8	1087.0	216.6	28.4	855.9
SD	17.0	2.2	12.5	99.0	11.0	350.9
IC 90	(289.6–301)	(36.1–37.5)	(1087–1091.2)	(183.4–249.8)	(24.7–32.1)	(738–973.7)

1716464: Table

	Part A	Part B			
PK Parameters	100 mg q2w	25 mg q4w	50 mg q4w	100 mg q4w	100 mg q2w
First dose					
n	14	31	28	29	29
C_{max} (μg/mL)	7.50 ± 2.91	1.86 ± 1.11	2.99 ± 1.51	6.73 ± 2.73	6.60 ± 3.03
T_{max} (day)[a]	3.9 (2.2, 13.8)	5.0 (2.9, 27.8)	5.4 (2.9, 12.6)	5.0 (3.0, 13.9)	4.9 (2.9, 10.7)
$AUC_{(t1-t2)}$ (day*μg/mL)[b]	80.63 ± 25.66	29.08 ± 10.65	49.38 ± 23.15	107.88 ± 43.05	66.03 ± 31.62
Last dose					
n	11	28	21	22	26
C_{max} (μg/mL)	20.01 ± 4.40	2.93 ± 1.29	4.26 ± 1.73	9.34 ± 4.31	15.68 ± 7.07
T_{max} (day)[a]	4.03 (3.0, 7.0)	4.0 (2.8, 11.7)	5.0 (0.0, 7.0)	4.0 (0.0, 7.1)	5.0 (0.0, 9.7)
$AUC_{(t1-t2)}$ (day*μg/mL)[b]	232.43 ± 48.90	52.02 ± 22.03	83.52 ± 35.17	172.04 ± 86.17	188.67 ± 90.43
$t_{1/2}$ (day)	18.32 ± 4.51	14.89 ± 4.54	16.12 ± 4.75	16.00 ± 4.11	19.01 ± 4.32
R_{Cmax}	2.67 ± 1.08	1.62 ± 0.57	1.66 ± 0.65	1.51 ± 0.87	2.55 ± 1.03
$R_{AUC(t1-t2)}$[b]	2.68 ± 0.52	1.68 ± 0.37	1.81 ± 0.65	1.57 ± 0.83	3.01 ± 1.23

[a]Median(Min,Max) reported for T_{max}. [b]AUC_{0-14d} and AUC_{0-28d} reported for q2w and q4w groups, respectively. R: accumulation ratio

administrations. Sirukumab PK in RA patients was generally consistent with that observed in healthy subjects.

1708491

The Impact of Drug-related QT Prolongation on FDA Regulatory Decisions

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Statement of Purpose, Innovation or Hypothesis: Since 2005, new drugs are evaluated for QT prolongation in a thorough clinical QT assay (TQT), per International Conference of Harmonization guideline (ICH E14). To date, over 500 drugs have been evaluated in this clinical assay. The purpose of the present exercise was to evaluate the regulatory outcome of drugs that tested positive in the TQT study.

Description of Methods and Materials: We used the FDA database to identify QT prolonging drugs that were evaluated within the period from May, 2006 to March, 2013. The following information was collected: magnitude of QT interval prolongation, therapeutic area, submission year, application status and safety warnings in approved drug labeling.

Data and Results: Forty-six (46) drugs were identified as prolonging the QT interval. The mean, minimum and maximum effect sizes were 17.1, 7.3 and 64.6 msec, respectively. We categorized drugs by magnitude of QT prolongation: QTc <10 msec, 10–20 msec and >20 msec: the percentages of drugs in each category were 26%, 49% and 26%, respectively. Forty-one of 46 drugs (89%) identified as prolonging the QT interval were approved. Five drugs were not approved; one application was withdrawn by the sponsor, and 4 received a Complete Response letter. The major reason for the Complete Response Letter was lack of efficacy; a QT-related safety concern led to a major deficiency for one drug. Of the 41 approved drugs, 3, 5 and 25 have QT-related Boxed Warnings, Contraindications, and Warnings and Precautions, respectively. For eight drugs, the QT effect was described in the study description provided in the label. Oncology and psychiatric indications were the most common indications (21 of 46) for drugs testing positive for QT prolongation.

Interpretation, Conclusion or Significance: Most drugs testing positive for QT prolongation in the TQT study were approved, with labeling to address the safety concern. Many of these drugs are indicated for oncology and psychiatry.

1709854

A Clinical Simulation Tool for Evaluating EMA's Regulatory PK Acceptance Limits for Bioequivalence Testing of Inhaled Corticosteroids

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Statement of Purpose, Innovation or Hypothesis: The European Medicines Agency (EMA) recommends a stepwise approach to demonstrate bioequivalence (BE) of inhaled corticosteroids (ICSs). Systemic bioequivalence (safety) should be demonstrated preferably by a pharmacokinetic (PK) study. If PK fails, then a pharmacodynamic (PD) study is allowed to demonstrate the systemic bioequivalence. However, since the PD response is determined by PK and a detailed PK/PD model is available, it was our interest to test whether regulatory BE limits accepted for PD can be back-translated into potentially wider PK BE acceptance limits.

Description of Methods and Materials: A clinical trial simulation tool was developed based on a previously published Emax-based suppression model. Crossover studies of test (T) and reference (R) inhaled Fluticasone Propionate, with various doses and numbers of subjects were simulated. The PK profiles and the corresponding suppressions of endogenous cortisol release (PD profiles) for both T and R were simulated. For each scenario, 1000 trials were simulated. The 90% confidence intervals for T/R ratios of AUC and Cmax (both PK and PD) in each trial were calculated. The percentage of trails passing the BE criteria (80–125%) for each scenario was calculated and was defined as the statistical power of the study design. Identification of the T product just passing the PD BE limits allowed re-assessment of the PK BE limits.

Data and Results: (1) The clinical simulation tool was validated by showing that the simulation results overlapped well with clinical data from literature. (2) The statistical powers achieved with different sample sizes were calculated. Based on the results, the statistical power is positively correlated with the sample size. (3) The 90% CIs of PK and PD in each trial were obtained. Results allowed to redefine the PK CI intervals

Interpretation, Conclusion or Significance: This clinical trial simulation tool can be used to correlate the width of the PK BE limits with that of PD BE limits. It can also be used to help design clinical trials for BE study of ICSs. The results from this project could impact the BE guidelines for ICSs of EMA.

1709912

Pivotal Role of Clinical Pharmacology In 505(b)(2) New Drug Applications

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Statement of Purpose, Innovation or Hypothesis: In addition to BA/BE assessments, many 505(b)(2) NDAs include other clinical pharmacology (CP) assessments unique to each drug product. The purpose of this review is to identify and report scientific and regulatory issues related to CP in 505(b)(2) NDAs to help applicants proactively address some of those issues in their applications.

Description of Methods and Materials: Approval letters, package inserts, CP reviews for 46 505(b)(2) NDAs approved in 2012 were obtained from Drugs@FDA and FDA internal database.

Data and Results: Among 96 original approved NDAs in 2012, 48% (46/96) were categorized as 505(b)(2) NDAs based on their approval letters. A review of the CP reviews of these 46 drug products indicated that 37% (17/46) of these NDAs were supported solely by a BA/BE assessment with no additional clinical safety/efficacy studies, 26% (12/46) included BA/BE and clinical safety/efficacy studies, and 17% (8/46) included a request for a biowaiver in the NDA and no human studies. Among 46 505(b)(2) NDAs, 6 NDAs were submitted for marketed, unapproved products, out of which 2/6 were approved based solely on literature based information and no human studies were conducted with the product, 1/6 was approved based on a BA/BE study and the rest of the 3 products were approved based on clinical efficacy/safety studies and some CP assessments. A review of the pre-NDA meeting discussion held for 50% (23/46) of these NDAs revealed that CP related topics discussed at these meetings (in no particular order) included study design and listed drug selection for BA/BE study, PK data format to be included in the NDA, population PK analysis to address effect of co-variates on drug exposure, bio-analytical assay for the drug and/or the metabolites, selection of the right reference product to employ in the relative BA/BE study, acceptability of literature based information to address missing gaps of information for some drugs, as well as biowaiver related discussion.

Interpretation, Conclusion or Significance: Our review indicates that the discipline of clinical pharmacology plays a significant and integral role in 505(b)(2) NDAs. In addition to typical BA/BE assessments, 505(b)(2) NDAs frequently include other CP assessments, literature based CP information, population PK analysis and occasionally data from *in vitro* assessments to address issues such as alcohol and other drug interactions. This information will help future 505(b)(2) applicants understand some of the CP considerations for their drug products.

1709845

Highly Active Antiretroviral Therapy-iInduced Dysglycemia in Human Immunodeficiency Virus-iInfected Patients at a Tertiary Referral Hospital

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Statement of Purpose, Innovation or Hypothesis: Dysglycemia is a major metabolic problem emerging in the treatment with Highly Active Antiretroviral Therapy. Comparision between four commonly used regimen in hospitals may provide important guide to clinicians in early detection of dysglycemia. It may provide early rescue from diabetes mellitus and hence may improve quality of life of patients infected with human immunodeficiency virus. Our study objetive was to compare dysglycemia between four regimens of highly active antiretroviral therapy routinely prescribed in King Edward Memorial Hospital Mumbai.

Description of Methods and Materials: Individual subject was interviewed in Human immunodeficiency virus out patient department of the institute from 31-Jan-2011 to 04-Aug-2011after the approval of institutional Ethics committee. Informed Consent was obtained from all subjects in written form. Total 219 Human immunodeficiency virus infected patients who are on one of the highly active antiretroviral therapy regimen for not less than six months were enrolled in the study. Those four regimens are 1)zidovudine,Lamivudine,Nevirapine 2) zidovudine,Lamivudine,Efavirenz 3)Stavudine,Lamivudine,Efavirenz 4)Stavudine,Lamivudine,Nevirapine. Investigation Fasting Blood Sugar and post lunch blood sugar was performed once for all subjects participating in the study and reports were collected at.Patients were evaluated according to American Diabetes Association. Descriptive and Inferential statistics were used. In descriptive statistics analysis, percentage mean and median values were calculated. For inferential statistics Kruscal-Wallis test was applied.

Data and Results: Data of 219 patients (150-Male & 69-Female) was collected.13 patients found as diabetic and the perentage of diabetes was 5.95%. Data was not normally distributed hence,for inferential statistics Kruscal-wallis test (non parametric ANOVA)was used. Test showed P value for fasting blood sugar and post lunch blood sugar comes out to be 0.2584 and 0.5240 respectively

Interpretation, Conclusion or Significance: Percentage of dysglycemia was higher in the regimen which included stavudine.This supports the previous study of stavudine associated insulin resistance.

1709845: Details of the patients found Diabetic in different regimens

Treatment Regimens	No of male patients	No of female patients	No of Diabetic Patients	Total Patients
Stavudine, Lamivudine, Nevirapine	36	18	04	54
Zidovudine, Lamivudine, Nevirapine	39	22	03	61
Stavudine, Lamivudine, Efavirenz	30	21	04	51
Zidovudine, Lamivudine, Efavirenz	36	17	02	53

1710611

Satisfaction of Healthy Subjects Participating in Phase I Clinical Trials

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Statement of Purpose, Innovation or Hypothesis: Satisfaction surveys provide clinicians valuable insight into quality of care metrics. Because a literature search did not reveal any published data on healthy subject satisfaction in clinical trials, we created a survey to address this deficiency.

Description of Methods and Materials: Subjects were healthy participants in bioequivalence (BE) clinical trials at Worldwide Clinical Trials Drug Development Solutions (WCT-DDS). Staff asked subjects to voluntarily take the 18 question survey anonymously at their last study

visit. Most survey questions evaluated trial satisfaction using a positive statement about the trial, and answers were ranked from 1 (strongly agree) to 7 (strongly disagree), with 4 being neutral. Demographic data was collected and two-sided T-tests were used to evaluate significant differences between demographic groups.

Data and Results: Between 90–95% of subjects asked to participate did so, with 181 healthy subjects completing the survey (97 male, 80 female, 4 non-identified; ages 18-55 years). Overall, subjects were very satisfied, with an average total score of 2.26 (SD = 0.68). Highest satisfaction was related to subjects having a clear understanding of clinical trials (mean = 1.36; SD = 0.81) and receiving enough time to review the informed consent (mean = 1.46; SD = 0.87). Lowest satisfaction was related to food (mean = 4; SD = 2.01), sleep (mean = 3.51; SD = 1.80) and stipend (mean = 2.75; SD = 1.38). Hispanic subjects found the informed consent more confusing (mean = 2.06) than non-Hispanics (mean = 1.59; p = 0.013). Other significant findings relate to education, gender, age and employment status. Subjects who previously participated in a clinical trial at another site reported greater satisfaction with their experience at WCT-DDS.

Interpretation, Conclusion or Significance: Subjects overall were satisfied with their experience and none were dissatisfied. Lower satisfaction with food may be due to study-related diet, and lower sleep satisfaction may result from sleeping in dormitory settings. Significant findings relating levels of satisfaction to various demographic variables suggest further study is warranted.

1710236

Oxidative Stress as a Cofactor in Spinocerebellar Ataxia Type 2

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Encore Presentation: *Mariela Guevara-Garciaa, Lizette Gil-del Valleb,*, Gregorio Martinez-Sanchezc, Luis Velasquez-Perezd. Altered redox status in Cuban patients with spinocerebellar ataxia type 2. Biomedicine & Aging Pathology 2 (2012) 24-29.*

Statement of Purpose, Innovation or Hypothesis: Spinocerebellar ataxia 2 (SCA2) is a clinically, pathologically and genetically neurodegenerative disorder. The number of clinical assays in these patients is limited because, among other factors, a lack of biomarkers for the assessment of the main clinical and genetic features of the disease and the evaluation of therapeutic options.

Description of Methods and Materials: The aim of this study was to investigate an extensive array of redox status indexes: glutathione (GSH), malondialdehyde (MDA), peroxidation potential, superoxide dismutase (SOD), ferric reducing ability of plasma (FRAP), catalase (CAT), total hydroperoxide (TH) and advanced oxidation protein products (AOPP) by spectophotometric techniques in relation to electrophysiogical markers in-Cubans SCA2 patients compared to those of healthy aged-gender matched control. The Pearson correlation between progression markers and oxidative stress indexes were assessed too.

Data and Results: Nineteen SCA2 patients' and 19 healthy subjects were recruited. Significant differences ($P < 0.05$) in PP, FRAP, GSH, SOD, AOPP and TH in SCA2 values were found relatively to the control group. The grade of oxidative reaction was evaluated as moderate to severe in almost markers for the studied group. Pearson significant correlation was found between PPLatMOS and FRAP-Lat.

Interpretation, Conclusion or Significance: These results contribute both to the evidences that oxidative stress occurs during spinocerebellar ataxia type 2 and its useful for the integral management of patient.

1717125

Identification of Proteins in Differentiated SH-SY5Y Neuroblastoma Cells Using Proteomics: 2D-Gel Electrophoresis and Mass Spectral Analysis

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Statement of Purpose, Innovation or Hypothesis: Opioids such as morphine are potent analgesics when treating chronic pain. However, long term use leads to the development of tolerance and severe side effects such as respiratory depression. The mechanism of morphine tolerance is not well understood and there are several that have been proposed. Research is being performed to target ways to prevent and/or reverse morphine tolerance with anti-opioid peptides such as Neuropeptide FF (NPFF). NPFF reverses the effects of morphine by inactivation of the opioid receptors through the activation of NPFF receptors. Proteomics-based approach would help identify proteins that may help elucidate the mechanism involved in developing morphine tolerance. The purpose of this study is to profile proteins in differentiated SH-SY5Y neuroblastoma cells.

Description of Methods and Materials: The cells were grown in DMEM/F-12 media at 37˚C, 95% air/5% CO2 and differentiated with 10 μM of retinoic acid (R.A.) for six days. The cells were chronically treated with 10 μM of morphine for 24 hours, .1 μM of NPFF analog 1DMe for 24 hours or pre-treated with .1 μM of 1DMe for 1 hour followed by 10 μM of morphine for 24 hours. The cells were lysed to extract proteins, the proteins were separated by 2-D gel electrophoresis and the gels were stained coomassie blue, and analyses were performed using PDQuest software. The spots selected for identification using matrix-assisted laser desorption/ionization - time-of-flight mass spectrometer (MALDI-TOF MS) showed significant changes between the treatment groups.

Data and Results: The proteins identified have roles in many cellular processes.

Interpretation, Conclusion or Significance: The results indicate that identification of proteins in differentiated SH-SY5Y neuroblastoma cells using proteomics may help in elucidating a mechanism for the development of morphine tolerance.

1717229

Detrimental Effects of Cocaine on Rat C6 Glial Cells Via Inflammation

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Statement of Purpose, Innovation or Hypothesis: INTRODUCTION: The usage of drug abuse substances has increased exponentially during the last decade and has become a more serious problem. All drugs have a negative effect on the nervous system, but few can match the dramatic impact of cocaine. Cocaine is one of the most potent, addictive, and unpredictable recreational drugs, and thus can cause the most profound and irreversible damage to the nervous system. In the other hand astroglial cells make up a large fraction of CNS cellular volume in humans, playing a predominant role in maintaining the health and viability of neurons. Nitric oxide (NO) is a key biosignaling molecule produced in both peripheral tissues and the central nervous system and

neurological injury and Alzheimer's disease are often associated with the increase of nitric oxide (NO) from resident glial cells in the brain. HYPOTHESIS: Cocaine cause cytokine expression and nitric oxide induction in stimulated glial cells a possible link to Alzheimer's disease

Description of Methods and Materials: We used rat cytokine array membranes to determine the change in rat C6 glial cell cytokine expression upon exposure to cocaine (2,4 and 7 mM) and also investigated effect of cocaine on production of nitric oxide by stimulation of C6 glioma cells with lipopolysaccharide Escherichia coli 0111:B4 and interferon gamma (LPS/IFN-g)

Data and Results: We found that after 24 hours cocaine exposure (2,4 and 7 mM), expression of vascular endothelial growth factor (VEGF), interleukin-1α (IL-1α), interleukin-1β (IL-1β), interleukin-10 (IL-10), interleukin-6 (IL-6), and interferon-γ, (IFN-γ) was substantially increased as compared to the non-treated control. Our finding of nitric oxide study confirmed cocaine role in inflammation in the presence of potent pro-inflammatory agent.

Interpretation, Conclusion or Significance: These findings suggest that the glial cells play a critical role in orchestrating inflammatory responses affected by cocaine which can contribute to the progression of neurodegenerative disease like Alzheimer's.

1708951

Payment Affirmation Algorithm: An Evidence-based Approach to Healthcare Reimbursement for High Cost Drugs for Life-threatening, Rare and Orphan Diseases

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Encore Presentation: *Abstracts of the American Society of Clinical Pharmacology and Therapeutics Annual meeting, Indianapolis, IN, March 9, 2013.*

Statement of Purpose, Innovation or Hypothesis: Many drugs have reached purchase costs that have attained potentially prohibitive levels of affordability. These agents, often indicated for rare, orphan, immunologic, and oncologic diseases, may potentially impact negatively on the financial viability of various health care systems if their use is inappropriate or unwarranted. A rationale, evidence-based decision process to guide use of these agents in certain health care systems is needed.

Description of Methods and Materials: The pharmaceutical data banks of a large national health maintenance organization were reviewed to select recent requests for reimbursement of several high cost therapeutic agents. A cooperative group of pharmacists, clinical pharmacologists and specialty clinical practitioners retrospectively applied criteria to the case information on which to base approval for drug reimbursement. Ten inordinately expensive drugs were selected for review without knowledge of approval for use status of the request.

Data and Results: A Payment Affirmation Algorithm (PAA) was proffered from group consensus criteria as a framework for affirming payment. Elements of the PAA included level of evidence base for approval, relative toxicity or efficacy of the drug, patient co-morbidities and anticipated longevity, coverage by contract plan, FDA approval, contraindications, potentially hazardous drug-drug interactions, experimental (off-label) status, and defined level of clinical improvement. Although 9 of the 10 drugs met Grade I evidence for efficacy, 2/3 were estimated not likely approvable on the PAA to justify payment for use.

Interpretation, Conclusion or Significance: Development, refinement and appropriate application of criteria for reimbursement of high cost pharmaceutical agents will be needed to insure viability of the health care system and promote rational, evidence-based treatment of patients. A decision-making algorithm for use in this setting should inculcate standard of care medical judgment, ethical considerations, sound pharmacological principles, economics and contractual agreement. The PAA developed in this study requires further testing and expansion of application to other therapeutic areas.

1708033

Type II Diabetes Mellitus in Children: Analysis of Prevalence Based on the Pediatric Health Information System Database

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Statement of Purpose, Innovation or Hypothesis: The purpose of this investigation was to determine the extent to which type II diabetes mellitus(T2DM) could be considered an "epidemic" based on prevalence amongst children less than 18 years old.

Description of Methods and Materials: The Pediatric Heath Information System(PHIS), an administrative database that contains inpatient, emergency department, ambulatory surgery and observation data from 43 non-for-profit, tertiary care pediatric hospitals in the United States, was utilized for this purpose. All patients with a diagnosis code for diabetes mellitus(ICD-9 250.x) were collected from 2004 to 2012 and patients were classified as either type I diabetes mellitus(T1DM) or T2DM based on their principal diagnosis code. Data was exported for analysis in SAS(v9.3). Prevalence was analyzed by geographical region, age, gender and obesity designation. The use of metformin across region, age group and diagnosis was compared.

Data and Results: The partition of T2DM by region was 32.75% from the North Central, 9.76% from the Northeast, 41.30% from the South and 16.18% from the West. Of the 30,192 T2DM patients, 2024 (6.70%) had a diagnosis code for a family history of diabetes(ICD-9 V18.0). There was not a significant change in T2DM prevalence by year; .15 to .22%. Of the T2DM patients, 5544(18.36%) patients had a diagnosis for overweight, obesity and other hyperalimentation. This is likely to be under-reported based on comparative analysis with external data. 10.71% of the patients with an admit diagnosis of T2DM changed to T1DM during their treatment and 0.59% of the patients with an admit diagnosis of T1DM changed to T2DM during their treatment.

Interpretation, Conclusion or Significance: These results are comparable to outpatient data collected from analysis of insurance data (third-party payer) and other commercial data stores. These results suggest that the prevalence of T2DM, while concerning, may not suggest the epidemic status originally described in the literature. Planned clinical trials for T2DM pediatric patients should keep this in mind when trying to identify an enrollable pediatric population.

1708033: Table

		Number (%)
Age Group	Neonates	14 (0.05)
	Infants	325 (1.08)
	Children	12057 (39.93)
	Adolescents	17796 (58.94)
Gender*	Male	12700 (42.06)
	Female	17479 (57.89)

*Missing, n = 13 (0.05%)

1714226

Etiology and Pharmacotherapy of Heart Failure in a Nigerian Tertiary Hospital

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Statement of Purpose, Innovation or Hypothesis: Heart failure imposes an escalating burden on healthcare budget and its prevalence is increasing globally.Data on heart failure etiology and treatment in Nigeria and Africa are sparse. We set out to determine the risk factors, causes, and treatment of heart failure among patients who attended the University of Nigeria Teaching Hospital Enugu, Nigeria from January 2008 to December 2010, a 3year period.

Description of Methods and Materials: The study was retrospective and involved retrieving folders of patients diagnosed of heart failure, aged 18 years and above from the medical records. Data on patients' personal profile, presentation, risk factors, etiology and treatment were collected and analyzed.

Data and Results: There were 360 patients with heart failure and males were more affected than females (1.7:1). The mean age was 59.23 yrs. The commonest causes of heart failure in this study were hypertension (56.6%), cardiomyopathy (7.4%), diabetes mellitus (4.9%), cor pulmonale (4.9%) and unknown causes (11.5%). Frusemide was used in all the patients. ACEI/ARB in 76%, Spirinolactone in 70%, Digoxin in 70%, anticoagulant in 12% of the prescriptions. No beta blockers, isosorbide dinitrate/hydralazine (ISDN/HYD) prescriptions were documented.

Interpretation, Conclusion or Significance: The causes of heart failure in this study are in keeping with findings in Nigerian and other African countries were non ischaemic factors are largely to blame. This differs from the ischaemic causes prevalent in Europe and USA. Despite compelling evidence of better outcome from AHeFT, and recommendations from current practice guidelines, ISDN/HYD remains underutilized in Nigerians and Africans with heart failure. There is increase in prevalence of cardiovascular risk factors, mainly hypertension, diabetes, and obesity, paving the way for the substrate to a new epidemic in the future- the ischemic heart disease in Nigeria. These factors will largely determine the future outlook of heart failure in Nigeria and Africa. There is a need to utilize evidence based pharmacotherapy to achieve improved outcome.

1716189

The Clinical Relevance of Pharmacogenetic Testing, A Literature Review

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Statement of Purpose, Innovation or Hypothesis: Background: Pharmacogenetics is the study of genetic influence on pharmacological response. Pharmacogenetic testing serves to identify the presence of genetic variants which may affect pharmacological outcomes. Literary evidence pertaining to the clinical relevance of pharmacogenetic testing has historically presented conflicting results and remains a topic of controversy. Objective: To determine the clinical relevance of pharmacogenetic testing.

Description of Methods and Materials: Methods: A literature search was conducted using EBSCO host and EMBASE using a variety of search terms pertaining to pharmacogenetic testing in the following medication classes: cardiovascular, oncologic, pain management, antiretroviral, and antidepressant. Results were limited to English, full text articles published between the 2005 and 2013. Human randomized control trials, prospective control trials, meta-analyses, reviews, retrospective and case studies were included. Selected articles were evaluated and assigned ratings based on level of evidence using validated SORT tool. A rating of "A" was assigned for high level of evidence, "B" for moderate level of evidence, and "C" for minimal level of evidence.

Data and Results: Results: Our literature search resulted in a total of twenty-one selected articles of interest. Of these articles we identified seven articles with an evidence rating of "A" and four articles with an evidence rating of "B".

Interpretation, Conclusion or Significance: Conclusion: According to our findings, pharmacogenetic testing is relevant to clinical practice in certain situations. Its use provides health care providers with additional information which may enable them to treat patients more efficiently by preventing adverse reactions and anticipating therapeutic responses. A lack of prospective randomized control trials, ethical concerns, and a lack of provider knowledge pertaining to pharmacogenetic testing remain as barrier to routine pharmacogenetic testing in clinical practice. Despite these barriers, the future of pharmacogenetic testing is promising and expected to be welcomed by those whom are concerned with providing optimal pharmaceutical care.

1709608

A Novel Study Design for Parallel Group Thorough QT Studies: The Nested Crossover for Positive Control

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Statement of Purpose, Innovation or Hypothesis: BACKGROUND: A Thorough QT/QTc (TQT) study to assess Cardiac Safety is now required, per ICH-E14, for every new drug as a condition for regulatory approval. INTRODUCTION: Drugs with long half-life or need for slow up-titration may require a parallel group (PG) design. Such studies, typically conducted in healthy volunteers (HV), may require c. 200-300 subjects. We describe a novel PG TQT study design which uses a much smaller sample size for PG TQT studies

Description of Methods and Materials: METHODS: A double-blind, double-dummy, placebo (PLA) and positive controlled TQT Study enrolled 120 healthy volunteers, randomized to Active Drug (ACT; G1) or PLA (G2). In compliance with the E14 guidelines, a positive control (moxifloxacin, MOX) was nested in the PLA group using a cross-over design: half of subjects (selected at random) were treated with MOX on Day 1 (G2a) and half on Day 15 (G2b). On Days 1–5 subjects received a single tablet/day (2 mg ACT or PLA). From Day 6 onwards the number of tablets increased with 1/day to 5 tablets (10 mg ACT or PLA) on Days 9–13 with a last intake of MOX (group 2b) or PLA (others) at Day 15. Twelve-lead 24-hour Holter ECGs were recorded on Days -1, 1, 5, 13 and 15. ECGs were extracted in triplicates at each time point and analyzed by a Core ECG Laboratory.

Data and Results: RESULTS: 68 males and 52 females were randomized, average age 29 yrs. The mean time-matched difference in study-specific QTc interval (QTcSS) between ACT and PLA was <5 ms at all assessed time-points for both doses. Moreover, the upper limits of the 90% CI were all below the regulatory threshold of 10 ms. There were no QTcSS values >450 ms or increases >60 ms during ACT treatment. The QTcSS exponents were close to the QTcF exponent. Assay sensitivity was established by demonstrating that the lower limit of the

90% CI of the estimated mean difference in QTcSS between MOX and PLA was >5 ms for all assessed time points between 2 h and 6 h.

Interpretation, Conclusion or Significance: CONCLUSION: A novel PG Nested-XO TQT study design was successfully completed, demonstrating assay sensitivity and enabling a sample size of half the magnitude of standard PG TQT studies and satisfying the regulatory requirements for cardiac safety.

1709719

Proton-pump Inhibitors are Associated With Hypomagnesemia - A Large-scale Community-based Cohort Study

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Statement of Purpose, Innovation or Hypothesis: In 2011, the FDA issued a drug safety communication on hypomagnesemia associated with proton pump inhibitors (PPIs), based on ±30 mostly hospitalized cases. Subsequently, 2 cohort studies in hospitalized patients found an increased risk of hypomagnesemia in PPI users. The purpose of this study was to examine the association between PPI use and hypomagnesemia in ambulatory subjects.

Description of Methods and Materials: Retrospective cohort study using data from all Maccabi Health Maintenance Organization clinics between 2007 – 2012. Subjects with ≥1 serum magnesium records and a complete record of medications dispensed over 1 year preceding the lowest magnesium concentration (index magnesium) were included. PPI use during the 4 months preceding the index magnesium was categorized as none or any, the latter subcategorized as casual (medication possession ratio, MPR < 0.75) or chronic (MPR ≥ 0.75 for 4, 8, or ≥12 months preceding the index magnesium). Hypomagnesemia and severe hypomagnesemia were defined as index magnesium ≤0.7 and ≤0.55 mmol/L, respectively.

Data and Results: Among 95,205 subjects, 23.6% used PPIs. Hypomagnesemia was present in 6.0% of subjects, who were older and had more comorbidities, concomitant medications, and recent hospitalizations (risk factors). The prevalence of any hypomagnesemia was 11.3% in PPI users and 4.1% in non-users (adjusted ORs = 1.66; 95% CI, 1.55-1.78), and of severe hypomagnesemia 1.4% in PPI users and 0.2% in non-users (adjusted OR = 3.79; 2.99-4.82). Among patients with risk factors, the prevalence of any hypomagnesemia was 15.2% in PPI users and 8.5% in non-users (adjusted OR, 1.68; 1.56-1.81), resulting in a number needed to harm of 15. The risk for severe hypomagnesemia was increased even with casual PPI use (adjusted OR: 2.87; 2.12-3.89), further rising with treatment duration >4 months (adjusted OR, 4.20; 2.94-5.99).

Interpretation, Conclusion or Significance: Even short-term PPI use is associated with hypomagnesemia in the community setting, and the risk increases with chronic use. Monitoring magnesium concentrations may be justified in selected PPI users with additional risk factors.

1710185

Efficacy, Safety and Tolerability of 13.3 mg/24 h Rivastigmine Patch in Patients With Severe Alzheimer's Disease With and Without Concomitant Memantine

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Encore Presentation: *These data were previously submitted to the Alzheimer's Association International Congress, taking place in Boston, USA from 13–18 July 2013.*

Statement of Purpose, Innovation or Hypothesis: The ACTivities of daily living and cognitION (ACTION) study demonstrated significant efficacy of 13.3 *versus* 4.6 mg/24 h rivastigmine patch on Severe Impairment Battery (SIB) and Alzheimer's Disease Cooperative Study-Activities of Daily Living scale-Severe Impairment Version (ADCS-ADL-SIV) in patients with severe AD. Regardless of dose or duration, 61% of the study population were on concomitant memantine. The effect of concomitant memantine use on efficacy, safety and tolerability of 13.3 mg/24 h patch compared with 13.3 mg/24 h patch alone was investigated.

Description of Methods and Materials: ACTION was a 24-week, randomized, double-blind (DB) study in severe AD (Mini-Mental State Examination [MMSE] score ≥3-≤12). In this retrospective analysis, patients randomized to 13.3 or 4.6 mg/24 h patch were subdivided according to whether they received ≥1 dose of concomitant memantine during the DB phase. The changes from baseline at Week 24 on SIB and ADCS-ADL-SIV with 13.3 *versus* 4.6 mg/24 h patch were compared using analysis of covariance (ANCOVA) with treatment, pooled center, memantine usage, and treatment-by-memantine as factors and baseline as a covariate. Incidences of adverse events (AEs) were recorded.

Data and Results: Memantine-treated patients were younger than those not receiving memantine (mean [standard deviation], 75.9 [8.79] and 78.8 [9.15] years, respectively), and had a lower MMSE at screening (8.6 [2.91] and (9.2 [2.88]). Significantly greater efficacy ($p < 0.05$) was observed with 13.3 mg/24 h *versus* 4.6 mg/24 h patch on SIB and ADCS-ADL-SIV in patients receiving concomitant memantine, and SIB in those not receiving memantine. Overall, ANCOVA analysis confirmed there was no significant interaction ($p > 0.1$) between treatment and memantine use on SIB and ADCS-ADL-SIV. The incidence of AEs was 71.4% with 13.3 mg/24 h patch and memantine, 79.7% with 13.3 mg/24 h patch without memantine, 74.7% with 4.6 mg/24 h patch with memantine, and 71.1% with 4.6 mg/24 h patch without memantine.

Interpretation, Conclusion or Significance: These data suggest benefit of 13.3 mg/24 h patch, regardless of concomitant memantine use, and demonstrate similar safety and tolerability of 13.3 mg/24 h patch in memantine-treated patients and those not receiving memantine.

1710213

Effect of Body Mass Index on the Efficacy, Safety and Tolerability of Higher-dose 13.3 mg/24 h Rivastigmine Patch in Severe Alzheimer's Disease

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Encore Presentation: *These data were previously submitted to the Alzheimer's Association International Congress, taking place in Boston, USA from 13–18 July 2013.*

Statement of Purpose, Innovation or Hypothesis: Investigate effect of body mass index (BMI) on treatment response with rivastigmine patch in patients with severe Alzheimer's disease (AD).

Description of Methods and Materials: The ACTivities of daily living and cognitION study was a 24-week, randomized, double-blind evaluation of 13.3 *versus* 4.6 mg/24 h rivastigmine patch in patients with

AD and Mini-Mental State Examination scores ≥3-≤12. In this sub-analysis, patients were grouped by baseline BMI (<30 or ≥30). The changes from baseline at Week 24 on AD Cooperative Study-Activities of Daily Living scale-Severe Impairment Version (ADCS-ADL-SIV) and Severe Impairment Battery (SIB) with 13.3 *versus* 4.6 mg/24 h patch were compared for each subgroup using analysis of covariance (ANCOVA) with treatment, pooled center, BMI, and treatment-by-BMI as factors and baseline as a covariate. Safety and tolerability were assessed.

Data and Results: Of 716 patients randomized, BMI data were available for 711 patients (<30, n = 588; ≥30, n = 123). Baseline demographics/characteristics were generally comparable; patients with BMI <30 were older than those with BMI ≥30 (mean [standard deviation] age 77.7 [8.81] and 73.9 [9.42], respectively). At Week 24, significant treatment differences in favor of 13.3 mg/24 h patch ($p < 0.05$) were seen on ADCS-ADL-SIV and SIB in the overall population, ADCS-ADL-SIV in patients with BMI ≥30, and SIB in patients with BMI <30. ANCOVA analysis demonstrated significant interaction between treatment and BMI on the ADCS-ADL-SIV ($p = 0.049$), but not SIB ($p > 0.10$). In both treatment groups, patients with BMI ≥30 showed numerically greater decline (ADCS-ADL-SIV and SIB) than those with BMI <30. Overall, the incidence of adverse events (AEs) was comparable (BMI <30, 73.4%; ≥30, 75.6%). In patients with BMI ≥30, AEs occurred more frequently with 13.3 (80.0%) than 4.6 mg/24 h patch (72.1%); in patients with BMI <30, incidences of AEs were comparable (73.5% and 73.3%, respectively).

Interpretation, Conclusion or Significance: BMI influenced outcomes on ADCS-ADL-SIV, with significantly greater efficacy observed with 13.3 *versus* 4.6 mg/24 h patch in patients with BMI ≥30. No marked differences in overall safety and tolerability of high-dose patch were observed when patients were grouped by BMI.

1710258

Long-term Safety, Tolerability and Efficacy of 13.3 mg/24 h Rivastigmine Patch in Patients With Severe Alzheimer's Disease

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Encore Presentation: *These data were previously submitted to the Alzheimer's Association International Congress, taking place in Boston, USA from 13–18 July 2013.*

Statement of Purpose, Innovation or Hypothesis: A 24-week, open-label extension to the ACTivities of daily living and cognitION (ACTION) study was designed to assess long-term safety, tolerability and efficacy of 13.3 mg/24 h rivastigmine patch in severe Alzheimer's disease (AD).

Description of Methods and Materials: Patients with severe AD (Mini-Mental State Examination score 3-12, inclusive at double-blind baseline) who completed the 24-week double-blind study (13.3 or 4.6 mg/24 h patch) could continue into the open-label extension (13.3 mg/24 h patch). Incidences of adverse events (AEs), serious AEs (SAEs) and discontinuation due to AEs were reported. At Week 48, change from baseline on AD Cooperative Study-Activities of Daily Living scale-Severe Impairment Version (ADCS-ADL-SIV) and Severe Impairment Battery (SIB), and ADCS-Clinical Global Impression of Change (ADCS-CGIC) score were summarized. Patients were grouped according to double-blind treatment.

Data and Results: Of 463 double-blind study completers, 397 entered the open-label extension, with 197 continuing on 13.3 mg/24 h patch and 199 up-titrated from 4.6 to 13.3 mg/24 h patch. Baseline demographics and characteristics were comparable. AEs and SAEs were reported by similar percentages of patients (AEs: 57.9% and 59.8%; SAEs: 16.2% and 16.1%, 13.3 and 4.6 mg/24 h, respectively). Discontinuation due to AEs was comparable (11.2% and 12.1%, respectively). Larger mean [standard deviation] changes from double-blind baseline were observed in patients switched from 4.6 to 13.3 mg/24 h patch on ADCS-ADL-SIV (−4.6 [8.73]) and SIB (−7.0 [16.56]), than those who continued to receive 13.3 mg/24 h (−3.9 [8.00] and −4.7 [16.84], respectively). ADCS-CGIC scores were comparable between patients who received 13.3 or 4.6 mg/24 h patch during double-blind treatment.

Interpretation, Conclusion or Significance: There were no clinically relevant differences in safety and tolerability between patients switched from 4.6 to 13.3 mg/24 h patch and those who continued to receive high-dose patch in the extension. Greater, but more variable, decline was observed in patients who had a delay in switching from 4.6 to 13.3 mg/24 h patch, compared with patients who received 13.3 mg/24 h patch for a total of 48 weeks.

1710492

Benefit-Risk of Invokana™ (Canagliflozin) in Patients With Renal Impairment - Regulatory Perspectives

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Statement of Purpose, Innovation or Hypothesis: To assess benefit-risk profile of canagliflozin in patients with moderate renal impairment (modRI) to support the regulatory approval decisions.

Description of Methods and Materials: Clinical data submitted to support the NDA for canagliflozin was used for the benefit-risk analysis in modRI patients (eGFR, as mL/min/1.73m2: 30 to <60; including sub-groups by median eGFR) for 100 mg and 300 mg QD doses. Change from baseline in HbA1c was the efficacy endpoint. Change in renal function (eGFR) from baseline and other renal-related adverse events (AE) were assessed for safety.

Data and Results: Dedicated trial in modRI patients (eGFR 30 to <50), showed modest placebo-subtracted HbA1c reductions of −0.30% and −0.40% with 100 mg and 300 mg QD dose, respectively. There were dose-dependent AEs related to intravascular volume depletion and renal function. In pooled safety data (eGFR < 60), proportion of patients with at least one volume depletion-related AEs were 2.5%, 4.7%, 8.1% with placebo, 100 mg and 300 mg canagliflozin, respectively. Proportion of patients who experienced at least one event of significant renal function decline (defined as an eGFR 30% lower than baseline) in dedicated modRI trial (defined as an eGFR 30% lower than baseline) was 6.9%, 18%, and 22.5% for placebo, 100 mg, and 300 mg, respectively. Comparatively, in a pooled population of modRI patients, the incidence of these events was lower but dose-dependence of increase in incident episodes of significant renal function decline compared to placebo was preserved. Within modRI, efficacy was primarily driven by >median-eGFR subgroup along with similar or higher renal related AEs in the two subgroups.

Interpretation, Conclusion or Significance: Recommended starting dose for Canagliflozin is 100 mg QD that can be increased to 300 mg QD based on tolerability and need for added benefit. While no dose adjustment is needed in patients with mild renal impairment (eGFR >= 60), the dose is limited to 100 mg QD in modRI patients with an eGFR of 45 to <60. Key recommendation of not approving Canagliflozin in

patients with an eGFR <45 was based on modest benefit but similar or greater risk of AEs in comparison to patients with eGFR of 45 to <60. Analysis conducted by FDA was pivotal for regulatory approval decisions for canagliflozin use in renal impairment.

1716305

Golimumab Drug Exposure-Safety Analysis Using Integrated Data From Seven Phase 3 Clinical Trials Following Intravenous or Subcutaneous Administration

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Statement of Purpose, Innovation or Hypothesis: To explore the correlation between golimumab exposure and the occurrence of all infections, serious infections, serious adverse events (SAEs), and malignancies after administration of IV or SC golimumab in patients with rheumatoid arthritis, psoriatic arthritis, or ankylosing spondylitis.

Description of Methods and Materials: This pharmacokinetic (PK)/safety analysis was performed by pooling data from seven Phase 3 IV/SC golimumab studies to investigate if there is any relationship between PK exposure and selected safety events. Seven Phase 3 studies (2 IV and 5 SC) in the golimumab rheumatology program were included to leverage data from a large number of patients over a wide range of dosing regimens (from 50 mg SC q4w to 4 mg/kg IV q12w). Established population PK models after SC and IV administration of golimumab were used to generate empirical Bayesian estimates of steady-state golimumab PK exposure metrics for individual patients. All infections, serious infections, SAEs, and malignancies were evaluated.

Data and Results: From the PK/safety analyses of the pooled SC & IV data as well as the SC or IV datasets separately, as systemic exposures to golimumab increased within the range of evaluated golimumab doses, there was no trend of increasing infections, serious infections or SAEs regardless of the of the number of safety events for all PK exposure metrics. For malignancies, it was observed that there was no difference in any of the PK exposure metrics for patients who had no malignancies vs. patients who had malignancies.

Interpretation, Conclusion or Significance: No correlation of the occurrence of safety events with golimumab PK exposure metrics were observed with regard to all infections, serious infections, and SAEs with SC or IV golimumab. There was also no correlation of PK golimumab exposure with malignancy occurrences. The data suggest that IV and SC golimumab dosing regimens evaluated in these Phase 3 studies have similar safety profiles.

1717208

Investigation on Antimicrobial Behaviors of the Guidonia Tomentosa (Roxb.) Kurz: Traditionally Used for the Management of Diverse Diseases

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Statement of Purpose, Innovation or Hypothesis: Natural products and their derivatives represent more than 50% of the drugs in clinical use in the world. One of the paramount reasons for pursuing natural products chemistry resides in the actual or potential pharmacological activities to be found in alkaloids, coumarins, flavonoids, glycosides, lignans, terpenoids etc. Since the advent of antibiotics in the 1950's, the use of plant derivatives as a source of antimicrobials has been virtually non-existent. In the investigation, aqueous and methanolic extracts of aerial parts viz. leaves, stems, and seeds of Guidonia tomentosa (Roxb.) Kurz were screened for antimicrobial activities against pathogenic bacterial and fungal cultures.

Description of Methods and Materials: The extracts were screened for antibacterial spectrum against *Bacillus subtilis, Escherichia coli, Proteus vulgaris, Pseudomonas aeruginosa, Salmonella typhimurium, Staphylococcus aureus; and for antifungal spectrum against Aspergillus niger, Candida albicans, Penicillium chrysogenum,* and *Saccharomyces cerevisiae*.

Data and Results: The results showed that aqueous extracts of leaves, stems, and seeds possessed maximum antimicrobial activities in comparison to methanolic extracts. All the extracts showed antimicrobial spectrum against all the microbial cultures. It was found that antimicrobial potential of aqueous extracts of leaves was prominent in comparison to aqueous extract of seeds, followed by aqueous extract of stems. The methanolic extracts of the plant also possessed the same pattern but was found to be less significant than aqueous extracts. The aqueous extract of leaves of the plant was found to be potent antimicrobial agents against *Bacillus subtilis* at minimum inhibitory concentration value 0.25 mg/ml while it was found to be less active against *Aspergillus niger* at minimum inhibitory concentration value 0.50 mg/ml.

Interpretation, Conclusion or Significance: With these evidences it is feasible to scientifically validate that aqueous and methanolic extracts of Guidonia tomentosa (Roxb.) Kurz had an effect on antimicrobial and could have the same effect in human diseases. The indigenously available medicines and technologies can prove an asset in the tropical and developing countries of the world. At the same time developed countries also can be benefited because of safety profile of the plant extracts and microbial strains agents.

1708641

A Sensitive LC-MS/MS Method for Determination of Ipamorelin in Human Plasma

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Statement of Purpose, Innovation or Hypothesis: Post-operative gastrointestinal (GI) dysmotility, including ileus, remains a clinical problem. Ghrelin, a hormone primarily synthesized in the oxyntic gland in the stomach, can modulate gastric motility and gastric acid secretion. In a rat model, ghrelin has been shown to resolve gastric post-operative ileus. Ipamorelin is a ghrelin receptor agonist and is available as an intravenous treatment. The purpose of this work was to develop and validate a sensitive and robust method for determination of Ipamorelin in human plasma to support an ongoing Phase II clinical study HT-IPAM-202 (NCT01280344).

Description of Methods and Materials: A protein precipitation procedure was used for sample cleanup. Ipamorelin and its internal standard (Ipamorelin-$^{13}C_6$, $^{15}N_2$) in the resulting supernatant were chromatographed on a C18 column with gradient elution using methanol and acetonitrile-based mobile phase solutions. Ipamorelin and its internal standard were detected using an API 4000 LC/MS/MS system under positive MRM mode.

Data and Results: The method was validated over a range of 5.00 to 960 ng/mL using a weighted (1/x) linear regression. The correlation coefficients for validation batches were 0.995 or better. The intra-batch accuracy (%Bias) ranged from −3.7 to 5.3% with a precision (CV%) range of 3.1 to 7.0%. The inter-batch accuracy ranged from −0.7 to 3.6% with a precision of 5.5 to 6.0%. Matrix effect was evaluated in six

different lots of blank human plasma at concentrations of 15.0 ng/mL with a variation of response (CV%) at 3.6%. The method is robust in the presence of lipemic and hemolytic samples and the stability of Ipamorelin in both plasma and whole blood has been established. Preliminary plasma concentrations and incurred sample repeat data will also be presented from the ongoing clinical study.

Interpretation, Conclusion or Significance: This method showed acceptable accuracy, precision, selectivity, stability, and reproducibility. The validated method is simple and reliable in supporting further drug development and clinical studies.

1714797

Down Regulation of Voltagedependent Anion Channel 1 and Glucose-related Protein (GRP78) by Carvedilol and Tocotreniol in Doxorubicin Mediated Cardiotoxicity

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Statement of Purpose, Innovation or Hypothesis: With an increasing population of cancer survivors, it is imperative to understand the treatment options available and outcomes for chemotherapy-related cardiomyopathy. Doxorubicin -based chemotherapy causes heart failure in approximately 5% of patients. The present study was designed to testify the hypothesis that the possible synergistic effect of carvedilol, a non-selective alpha 1 and beta adrenergic antagonist and tocotrienol on cardiomyocyte apoptosis in doxorubicin induced rats.

Description of Methods and Materials: Our study revealed that mitochondrial outer membrane channel protein voltage dependent anion channel 1 and glucose regulated protein (GRP78) was exclusively upregulated during myocardial infarction, which is an important upstream regulator of the endoplasmic reticulum (ER) stress pathway after the administration of doxorubicin. Immunohistochemical and double-immunofluorescent stainings were performed to detect the expression of 78 kDa glucose regulated protein (GRP78), a marker of activation of the unfolded protein response. Immunoblotting analyses were performed to quantify GRP78 in the plasma of carvedilol and tocotreniol treated rats.

Data and Results: Carvedilol and tocotreniol combined effect has potential in managing cardiomyopathy through downregulating the membrane channel proteins, activated endoplasmic reticulum stress and apoptosis in the myocardium.

Interpretation, Conclusion or Significance: It was concluded that carvedilol and tocotreniol is a potential candidate to protect against acute doxorubicin cardiotoxicity, a major and dose-limiting clinical problem.

1707014

Estrogen Receptor Alpha-mediated Autophagy and Its Potential Significance in Thyroid Cancer Treatment

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Statement of Purpose, Innovation or Hypothesis: Human thyroid cancer occurs three times more frequently in females than in males. There is considerable laboratory experimental and animal evidence supporting that the development of human thyroid cancer is closely associated with the female sex hormones such as estrogen (E2). Although estrogen receptor alpha (ERa) has been supposed to mediate the proliferation-promoting effect of E2 on thyroid cancer cells, the exact molecular mechanism underlying is unclear.

Description of Methods and Materials: We employed RT-PCR and Western blot to measure ERa in human normal thyroid cells and thyroid cancer cells. The role of ERa was explored by assessing cell proliferation and autophagy. Relevant molecules were determined to explain the ERa-mediated changes in proliferation and autophagy.

Data and Results: Our data showed that the expression of ERa was increased in human thyroid cancer cells compared with normal thyroid cancer cells. Enhancement of the ERa level by DNA transfection or ERa agonists could significantly induce the proliferation thyroid cancer cells. Surprisingly, autophagy in thyroid cancer cells was also increased by such treatments. Further experiments showed that ERa enhanced autophagy in thyroid cancer cells via activating MAPK/ERK to modulate mTOR, a critical regulator of autophagy induction. ERa also down-regulated Bcl-xl to release Beclin1, an essential pro-autophagy protein. The promotive role of ERa was confirmed using tamoxifen, an antagonist of ERa, as tamoxifen was able to inhibit ERa-mediated autophagy and proliferation. A similar result was also obtained when ERa was knocked down by siRNA.

Interpretation, Conclusion or Significance: Autophagy is known to contribute to the development in some cancers, and it can also facilitate the resistance of cancers to chemotherapy and radiation treatment. Therefore, we conclude that the ERa-mediated autophagy contributes to the proliferation and growth of human thyroid cancer cells, suggesting the downregulation of autophagy may be a potential therapeutic strategy in treatment of thyroid cancer.

1707680

Predictivity of Nonclinical Repolarization Assay Data for Clinical TQT Data in FDA Database

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Statement of Purpose, Innovation or Hypothesis: Drug-induced QT interval prolongation and Torsades de Pointes remain serious public health issues when new pharmaceuticals are brought to the market place. Under the auspices of ILSI-HESI, a consortium involving representatives from industry, academia and government sought to assess the predictivity of non-clinical repolarization assays in relation to clinical measures of QT interval prolongation. This presentation will provide a final analysis of the predictivity of data from TQT studies and nonclinical studies submitted to support marketing approval of >150 new pharmaceuticals.

Description of Methods and Materials: A retrospective analysis of data from NDA and IND applications was conducted by the HESI Consortium. Study dates ranged from 1992–2011. Data from all drugs were blinded with respect to compound identity and absolute values and housed in the US FDA database. Three non-clinical safety pharmacology studies were selected to assess clinical predictivity: *in vitro* hERG channel assay, action potential duration assay in isolated cardiac tissue, and *in vivo* animal QT study.

Data and Results: A total of 150 drugs (91 NDAs and 59 INDs) were included in the database: 144 drugs with a TQT study, 141 with a hERG study, 85 with an APD study and 90 with a nonclinical ECG study. Analyses conducted include sensitivity, specificity, and concordance per assay type. An integrated analysis was also performed to determine sensitivity, specificity and concordance collectively across the assays. The results suggest that a robust nonclinical risk assessment provides reasonable predictivity when the clinical QT signal is of sufficient magnitude (>10 ms).

Interpretation, Conclusion or Significance: This program provides novel insights into the sensitivity and specificity of real data considered by the regulatory community and the analysis is a first of its kind to collectively assess preclinical to clinical predictivity of data submitted to a regulatory agency as part of drug development. The results have important implications for translating nonclinical data to the clinic.

1709165

Interferon-alpha Response Element Found for the B-cell Translocation Gene on Human Chromosome 21

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Statement of Purpose, Innovation or Hypothesis: Down syndrome (DS) is caused by the presence of an extra chromosome 21 (trisomy 21). There is currently an ongoing search for genes that are candidates for involvement in the learning difficulties associated with DS. On chromosome 21, there are genes that code for the components of the interferon (IFN) receptors. The presence of these genes would predict a fifty percent increase in the sensitivity of trisomy 21 cells to the action of the IFNs. However, trisomy 21 cells are found to be 10 to 15 times more sensitive to the IFNs than are euploid cells. We hypothesize that this excess sensitivity may be due to the presence of genes on chromosome 21 that are upregulated by the IFNs.

Description of Methods and Materials: We used the online PubMed gene databank to look for known IFN regulating sequences near chromosome 21 genes that are over expressed in DS brains. Only sites with contiguous base pair homology were considered for final analysis.

Data and Results: Consistent with the above hypothesis, we found an Interferon-alpha Stimulated Response Element (ISRE) 2,676 bp upstream of the chromosome 21, B-cell translocation gene (BTG3). This ISRE is the one used by IFN to control the indoleamine 2,3-dioxygenase gene (INDO). In addition, we found a Gamma-interferon Activating Sequence (GAS) used for the guanylate-binding protein (GBP) further upstream of the transcription start site (TSS) (shown in the table below).

Interpretation, Conclusion or Significance: The BTG3 gene is important in neurogenesis and thus, becomes a new candidate gene that could be involved in the learning difficulties seen in the DS patients. The finding of this gene with an IFN regulatory sequence on chromosome 21 supports the hypothesis that genes that are the target of IFN action may contribute to the excess IFN sensitivity of the trisomy 21 cell. If this gene is controlled by IFN, it may not be necessary to develop therapeutics specifically aimed at the BTG3 gene product. Pharmacotherapeutics designed to modify the action of IFN already in clinical trials may be useful for the amelioration of the effects of this over expressed gene.

1709165: BTG3 gene: Total Length: 19,300

Known Sites	Sequence Found	Position Near TSS
ISRE: INDO	TGGTTTCATTTTC	18, 987, 944
GAS: GBP	TTACTCTAA	19, 023, 224

1710660

Differential Effect of IV Iron Compounds on Intracellular Labile Iron Pool in Aortic Coronary Endothelial Cells

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Statement of Purpose, Innovation or Hypothesis: Cardiovascular disease is the leading cause of death for end-stage renal disease (ESRD) patients. This is likely due to oxidative stress, inflammation and changes in cellular signaling that are potentially exacerbated by IV iron administration. The available IV iron compounds have different stability profiles. The purpose of this study was to investigate whether available IV iron products induce changes in the intracellular labile iron pool in coronary endothelium.

Description of Methods and Materials: Rat aortic coronary endothelial cells (RACEC) were cultured in 96-well tissue culture plates. RACEC were treated with 0.05 mg/mL and 0.025 mg/mL concentrations of, Venofer® (iron sucrose, IS) Feraheme® (ferumoxytol, FMX), INFed® (iron dextran, IID), Dexferrum® (iron dextran, DID), or Ferrlecit® (sodium ferric gluconate, SFG) for 30 minutes. Intracellular labile iron was measured by fluorescence quenching, using Phen Green™ SK (20 μM) for 20 minutes. Fluorescence values are reported as mean $\pm$ SD fluorescence intensity. All experiments are $n \geq 4$.

Data and Results: Incubation of RACEC with all IV iron compounds at 0.05mg/ml, which is equivalent to approximate plasma concentrations achieved with a clinically relevant dose of 300 mg, were compared to control (408 ± 31 vs. 517 ± 42, $p = 0.007$), (441 ± 36 vs. 517 ± 42, $p = 0.03$), (421 ± 33 vs. 517 ± 42, $p = 0.01$), (423 ± 31 vs. 517 ± 42, $p = 0.01$), and (458 ± 27 vs. 517 ± 42, $p = 0.07$) respectively. Incubation with all iron compounds at 0.025 mg/ml were also compared to control (465 ± 37 vs. 517 ± 42, $p = 0.11$), (584 ± 49 vs. 517 ± 42, $p = 0.08$), (475 ± 41 vs. 517 ± 42, $p = 0.19$), (531 ± 44 vs. 517 ± 42, $p = 0.66$), and (447 ± 32 vs. 517 ± 42, $p = 0.039$) respectively.

Interpretation, Conclusion or Significance: At the 0.05 mg/mL concentration all iron compounds increased the intracellular labile iron pool. Implications of increasing the intracellular labile iron pool include disruption of normal cell signaling and intracellular oxidative stress. At the 0.025 mg/mL dose only FMX and DID, the most stable and largest molecular weight agents did not increase the intracellular labile iron pool. This has important clinical relevance as IV iron is being used more aggressively (e.g. higher single dose administration) in patients with ESRD. These data warrant further studies on derangement of the intracellular labile iron pool with IV iron products.

1716659

Sonographic Assessment of theToxicological Effects of Chronic Exposure to Petroleum Products on the Liver in Nigerians

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Statement of Purpose, Innovation or Hypothesis: Given the widespread use and abuse of petroleum products in a background of increasing hepatic diseases in Nigeria and globally, it is important to identify other methods apart from biochemical assays of assessing the toxicity of these products. The aim of the study was to investigate the effects of chronic low level exposure to petrol products on the liver of apparently healthy volunteer petrol station attendants, petrol tanker drivers and auto mechanics in Enugu, Nigeria using sonography.

Description of Methods and Materials: The study involved recruiting 415 exposed workers consisting of 164 petrol station attendants, 175 automobile mechanics and 76 petrol tanker drivers and 415 age and socio-economic class matched unexposed persons as control. All subjects met the inclusion criteria. Informed consent was obtained from all the participants and ethical clearance was given by the Ethics Committee of the University of Nigeria Teaching Hospital, Enugu. Sonography of the liver of the participants were done to note and classify sonographic changes. Biochemical assessments were also done to assess their liver function. Descriptive statistics, Fisher's exact test, Chi-square and t-tests were used to analyze the data at $p \leq 0.05$.

Data and Results: Statistically significant increase in the liver parenchymal echogenicity was seen in 16.87% of exposed workers compared with 2.17% of control ($p \leq 0.05$). Significant increase ($p \leq 0.05$) in the liver size was also noted among the exposed workers compared to the control (151 ± 0.61 mm vs 140 ± 0.56 mm respectively). More sonographically detectable morphological effects were noted among the automobile mechanics when compared with other exposed group ($p \leq 0.05$). Sonography also noted that out of 16.87% ($N = 70$) exposed workers with abnormal liver echopattern, only 2.65% ($N = 11$) had abnormal alanine transaminase suggesting that biochemical assessment may have underestimated toxicity.

Interpretation, Conclusion or Significance: The result of the study revealed evidence of ultrasound detectable hepatotoxicity among the exposed subjects. Ultrasound appeared to be a more sensitive tool than biochemistry in the detection of petroleum induced liver toxicity.

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Echocardiographic Assessment of Left Ventricular Function in Thyrotoxicosis Patients in Nigeria: Possible Therapeutic Implications

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Statement of Purpose, Innovation or Hypothesis: Thyrotoxicosis is an endocrine disorder with cardiovascular manifestations. A sound knowledge of its effect on the heart is indispensable in the management of this endocrine-vascular disease. We set out to study patients with thyrotoxicosis and to evaluate the effect of this disorder on the left ventricular function.

Description of Methods and Materials: Fifty patients who through clinical assessment and thyroid function tests were diagnosed thyrotoxic were recruited at the outpatient department of the University of Nigeria Teaching hospital Enugu, Nigeria. Echocardiography was done to assess Left ventricular systolic and diastolic function.

Data and Results: Thyrotoxicosis patients were leaner, had no significant difference in blood pressure when compared with controls. Eight patients were in congestive heart failure (5 had LVEF < 50%-systolic heart failure; and 3 had normal LVEF but impaired diastolic function-diastolic heart failure). There were significantly prolonged Left ventricular IVRT (in 28% of the patients), EDT (in 28%), reduced E/A ratio (in 34%) and PFR (in 34%) in thyrotoxicosis patients when compared with values obtained from the control (p value <0.01) in keeping with impaired diastolic dysfunction. The patients studied also had significantly enhanced left ventricular systolic function when their FS (43.9%-$p < 0.05$), CO (7.15l/min-$p < 0.05$), and AOVMAX (144cm/sec-$p < 0.05$) were compared with controls.

Interpretation, Conclusion or Significance: Enhanced systolic function is perhaps the earliest echocardiographic detectable heart disease and in keeping with the hyperdynamic circulatory state of thyrotoxicosis. Impaired diastolic dysfunction appears to be found in a majority of patients with thyrotoxicosis even among asymptomatic patients. These have therapeutic implications. The finding of diastolic dysfunction in asymptomatic thyrotoxicosis patients could be considered a risk factor for the future development of heart failure and the early identification of such patients using echocardiography provides a window of opportunity for therapy directed towards preventing progression of what appears to be preclinical heart disease