PI-160

A POPULATION PHARMACOKINETIC MODEL FOR PENTADECANOIC ACID (PA) AND TRIHEPTADECANOIC ACID (THA) EXPOSURE FOLLOWING ADMINISTRATION OF A MALABSORPTION BLOOD TEST (MBT) TO QUANTIFY STEATORRHEA. J. Mondick, J. Barrett, J. Schall, M. Mascarenhas, V. Stallings, The Children's Hospital of Philadelphia, Philadelphia, PA.

BACKGROUND: Metabolism of THA to heptadecanoic acid (HA) requires pancreatic lipase, which is known to be deficient in cystic fibrosis (CF) patients. We developed a preliminary pharmacokinetic model to explore the PA and HA time course following administration of the MBT. We will use this model to develop guidance on MBT administration and optimal sampling for discerning the degree of fat malabsorption.

METHODS: A retrospective analysis was performed using plasma concentrations from 31 healthy and 11 CF subjects. Data were analyzed via nonlinear mixed effect modeling using NONMEM.

RESULTS: The structural pharmacokinetic model was based on 2 compartments with first order elimination, Weibull absorption kinetics, and a term for endogenous PA and HA levels. The HA bioavailability in CF patients relative to healthy subjects was 42.4%. Mean (CV%) HA population estimates for V_c, k_e, k_{12}, k_{21}, and k_a were 17.2 (50.8) L, 0.596 (85.8) hr^{-1}, 0.439 hr^{-1}, 0.0330 hr^{-1}, and 0.336 (37.7) hr^{-1}. Fasting, enzyme administration and the presence of CF significantly affected the HA absorption rate.

CONCLUSIONS: This preliminary model provides good prediction for systemic PA and HA exposure following administration of the MBT to healthy subjects and CF patients. We are conducting additional studies to further improve the model to predict exposure in pediatric populations and refine the influence of gastric emptying on the absorption process.

PI-161

EFFECT OF FOOD OR ANTACID ON FEBUXOSTAT PHARMACOKINETICS AND PHARMACODYNAMICS IN HEALTHY SUBJECTS. R. Khosravan, PhD, B. Grabowski, BA, J. T. Wu, PhD, N. Joseph-Ridge, MD, L. Vernillet, PharmD, PhD, TAP Pharmaceutical Products Inc., Lake Forest, IL.

Febuxostat is a novel non-purine selective inhibitor of xanthine oxidase (NP-SIXO) being developed for the management of hyperuricemia in patients with gout.

AIM: The effects of food and antacid on oral febuxostat pharmacokinetics (PK) and pharmacodynamics (PD) were evaluated.

METHODS: In 4 phase-1, two-period, crossover studies, male and female subjects received either a single dose (SD) of 40 mg (n=23) or 120 mg (n=19), or multiple dose (MD) 80 mg daily for 6 days (n=23) of febuxostat under non-fasting [test (T)] and fasting [reference (R)] conditions; or received a single 80 mg dose with (T) and without (R) an antacid (800 mg $Mg(OH)_2$-900 mg $Al(OH)_3$). Plasma febuxostat (LC-MS/MS method) and serum uric acid (sUA, PD marker, enzymatic assay) concentrations were assessed.

RESULTS: A delay of t_{max} was observed with both food and antacid. Point estimates (PE) and confidence intervals (CI) for T and R ratios/differences are shown below for febuxostat C_{max}, AUC and sUA 24-hour mean concentration ($C_{mean,24}$).

Febuxostat Dose	Febuxostat C_{max}	Febuxostat AUC[1]	$C_{mean,24}$ (%)
Food Effect			
40 mg SD	0.54 (0.48–0.61)[2]	0.81 (0.77–0.85)[2]	-
80 mg MD	0.51 (0.44–0.60)[2]	0.82 (0.78–0.87)[2]	6 (4–10)
120 mg SD	0.62 (0.52–0.74)[2]	0.84 (0.79–0.90)[2]	-
Antacid Effect			
80 mg SD	0.68 (0.58–0.79)[2]	0.85 (0.81–0.90)[2]	-

[1] AUC_∞ [single dose (SD)] or AUC_{24} [multiple dose (MD)]; [2] T/R ratio PE (90% CI, log-transformed data) for febuxostat PK parameter ratios; [3] T-R difference PE (95% CI) for the % change from the baseline in $C_{mean,24}$.

Even though food caused a decrease in the absorption rate and extent of febuxostat in all food effect studies, this decrease was not associated with a decrease in febuxostat PD effect (sUA), when evaluated in the 80 mg MD study. Despite a decrease in the absorption rate of febuxostat, antacid had no effect on the extent of febuxostat absorption. Febuxostat was safe and well tolerated in all studies.

CONCLUSION: Febuxostat can be administered regardless of food or antacid intake.

PI-162

EFFECTS OF AGE AND GENDER ON FEBUXOSTAT PHARMACOKINETICS, PHARMACODYNAMICS, AND SAFETY IN HEALTHY SUBJECTS. R. Khosravan, PhD, M. Kukulka, BS, J. T. Wu, PhD, N. Joseph-Ridge, MD, L. Vernillet, PharmD, PhD, TAP Pharmaceutical Products Inc., Lake Forest, IL.

BACKGROUND: Febuxostat is a novel non-purine selective inhibitor of xanthine oxidase (NP-SIXO) being developed for the management of hyperuricemia in patients with gout.

AIM: The effects of age and gender on the pharmacokinetics (PK), pharmacodynamics (PD), and safety of febuxostat were evaluated.

METHODS: In a phase-1, parallel group, open-label, multiple dose study, male (M) and female (F) subjects between 19–40 years old [young (Y), 12M/12F] and 65–76 years old [elderly (E), 12M/12F] received once daily 80 mg oral doses of febuxostat for 7 days. Blood samples were collected to assess the PK of febuxostat and its active metabolites (67M-1, 67M-2, 67M-4) as well as its effect on uric acid (PD marker). Protein binding and safety of febuxostat were also assessed.

RESULTS: The results are shown in the table below.

Mean ± SD Plasma Pharmacokinetic and Serum Uric Acid (sUA) Parameters on Day 7

		Age		Gender	
Analyte	**Parameter**	**Y**	**E**	**M**	**F**
Febuxostat	$C_{max,u}$ (ng/mL)	28±12	27±9	24±10	31±10[1,2]
	$AUC_{24,u}$ (ng · h/mL)	56±19	61±20	54±23	63±15[1,2]
	f_u (%)	0.7±0.1	0.7±0.2	0.7±0.1	0.7±0.1
67M-1	AUC_{24} (ng · h/mL)	225±63	265±84	224±68	265±80
67M-2	AUC_{24} (ng · h/mL)	229±76	243±69	240±81	232±63
67M-4	AUC_{24} (ng · h/mL)	235±77	270±125	223±70	281±125
sUA	$C_{mean,24}$ (%change)	−55±8	−56±9	−52±7	−59±8[1]

$C_{max,u}$ or $AUC_{24,u}$: Unbound C_{max} or AUC_{24}; f_u: Unbound fraction; $C_{mean,24}$: sUA 24-hour mean concentration; [1]Statistically significantly different from M ($p \leq 0.05$); [2]Not statistically significantly different from M ($p > 0.05$) with weight as a covariate.

The overall incidence of study drug related adverse events (AEs) was lower in M than in F (13% vs 54%) and in Y than in E (25% vs 42%). The most common AEs were headache and constipation. The majority of AEs were mild in severity.

CONCLUSION: Neither age nor gender had any clinically significant effect on the PK, PD, and safety of febuxostat. Therefore, febuxostat does not require any dose adjustment based on age or gender.