

PI-160

A POPULATION PHARMACOKINETIC MODEL FOR PEN-
TADECANOIC ACID (PA) AND TRIHEPTADECANOIC ACID
(THA) EXPOSURE FOLLOWING ADMINISTRATION OF A
MALABSORPTION BLOOD TEST (MBT) TO QUANTIFY STE-
ATORRHEA. 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 pharmaco-
kinetic 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 kinet-
ics, and a term for endogenous PA and HA levels. The HA bioavail-
ability 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 signif-
icantly 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.

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

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

AIM: The effects of food and antacid on oral febuxostat pharma-
cokinetics (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 AUC₂₄ [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 associ-
ated 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 absorp-
tion. 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 PHAR-
MACOKINETICS, 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 evalu-
ated.

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**

| Analyte | Parameter | Age | | Gender | |
|------------|---------------------------------|---------|---------|---------|----------------------|
| | | 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 AUC₂₄; f_u : Unbound fraction;
 $C_{mean,24}$: sUA 24-hour mean concentration; ¹Statistically significantly different
from M (p ≤ 0.05); ²Not 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 major-
ity of AEs were mild in severity.

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