NCT #05365451

Pharmacokinetic drug-drug interaction study to identify biomarkers of kidney transporters

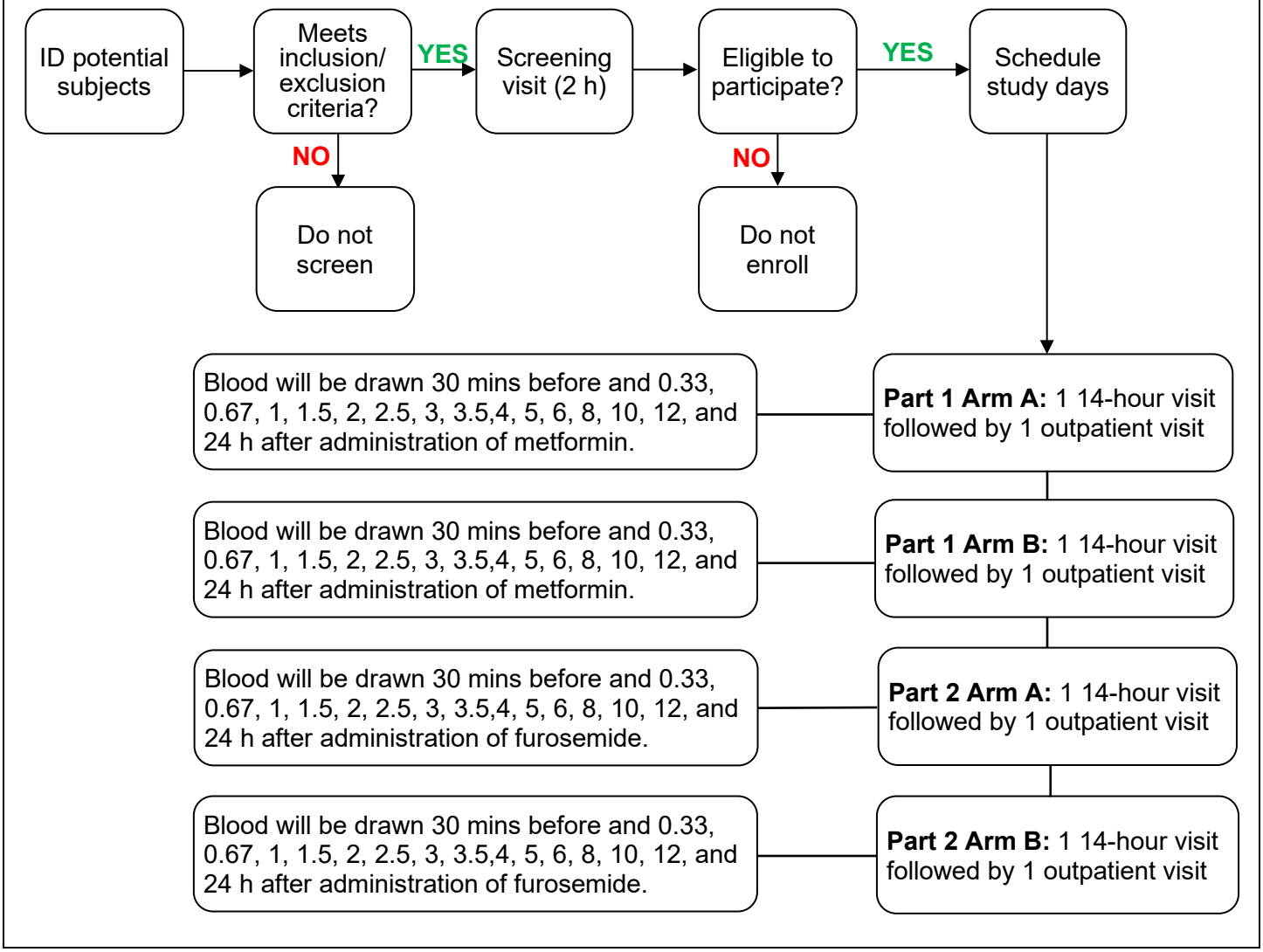
PI: Mary F. Paine, RPh, PhD

6/27/2025

College of
Pharmacy and
Pharmaceutical Sciences
WASHINGTON STATE UNIVERSITY

STUDY PROCEDURES FLOWCHART

***FIGURE 1**. Overview of procedures.*



SUBJECTS

Healthy non-smoking adult volunteers (8 men and 8 women) will be recruited from the local community to participate in this drug-drug interaction study (***FIGURE 1***).

PRE-SCREENING

Inclusion criteria:

- Aged from 18-64 years and healthy
- Not taking any medications (prescription and non-prescription) or dietary/herbal supplements known to alter the pharmacokinetics of any of the study drugs
- Willing to abstain from consuming dietary/herbal supplements and citrus juices for several weeks
- Willing to abstain from consuming caffeinated beverages or other caffeine-containing products the evening before and morning of the first day of a study arm
- Willing to abstain from consuming any alcoholic beverages for one day prior to any study day, during the 14-hour inpatient days, and for the outpatient visit(s) following the 14-hour visit
- Willing to use an acceptable method of contraception that does not include oral contraceptive pills or patches (such as abstinence, copper IUD, condom)
- Have the time to participate

- Written informed consent (and assent when applicable) obtained from subject or subject's legal representative and ability for the subject to comply with the requirements of the study

Exclusion criteria:

- Under the age of 18 or over the age of 65 years
- Smoke/vape/chew tobacco products
- Use cannabis products, including marijuana, hemp, and other THC- or CBD-containing products
- Have any current major illness or chronic illness such as (but not limited to) kidney disease, hepatic disease, diabetes mellitus, hypertension, coronary artery disease, chronic obstructive pulmonary disease, cancer, or HIV/AIDS
- History of anemia or any other significant hematologic disorder
- History of drug or alcohol addiction or major psychiatric illness
- Pregnant or nursing or plan to become pregnant within 3 weeks after participation
- History of allergy to metformin, cimetidine, furosemide, or probenecid
- Taking concomitant medications, both prescription and non-prescription (including dietary supplements/herbal products), known to alter the pharmacokinetics of any study drug
- Presence of a condition or abnormality that, in the opinion of the Investigator, would compromise participant safety or quality of the data
- Out-of-range clinical laboratory value that the study physician considers participation in the study a health risk

SCREENING VISIT

Potential eligible subjects, based on the inclusion/exclusion criteria, will present for a screening visit at the Nursing or Health Sciences Building on the Spokane campus. Informed consent will be obtained after full explanation of the study protocol. Consented subjects will undergo the following:

- A medical history and physical exam
- CBC with differential, electrolytes, liver function tests, serum creatinine
- Routine urine analysis
- Urine pregnancy test for female subjects of child-bearing potential (prior to enrollment in the study and prior to each phase of the study using in-home urinalysis pregnancy screens)

STUDY DESIGN

This study will consist of two Parts, each with 2 Arms (***FIGURES 2 and 3***). Each Arm will include one 14-hour inpatient visit and one outpatient visit. Subjects will undergo a washout period of at least seven days after completing each Arm. Subjects will be administered the following:

Part 1 Arm A: metformin (50 mg) by mouth as a liquid

Part 1 Arm B: cimetidine (400 mg) by mouth as a tablet, then one hour later, metformin (50 mg) by mouth as a liquid

Part 2 Arm A: furosemide (5 mg) by mouth as a liquid

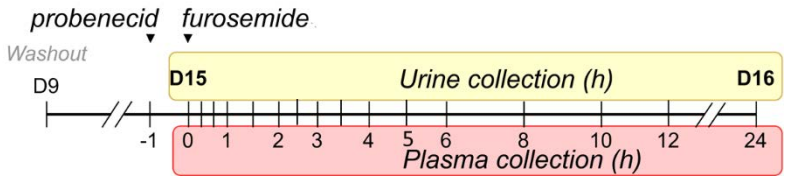
Part 1 Arm B: probenecid (1,000 mg) by mouth as a tablet, then one hour later, furosemide (5 mg) by mouth as a liquid

FIGURE 2. *Overview of study design.*

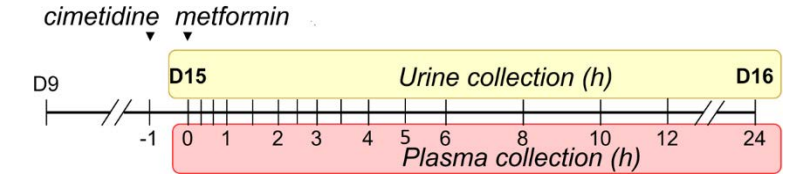
Screening	≥1 week washout	Part 1 Arm A	≥1 week washout	Part 1 Arm B
Screening	≥1 week washout	Part 2 Arm A	≥1 week washout	Part 2 Arm B

FIGURE 3. *Detailed timelines of the sequential arms.*

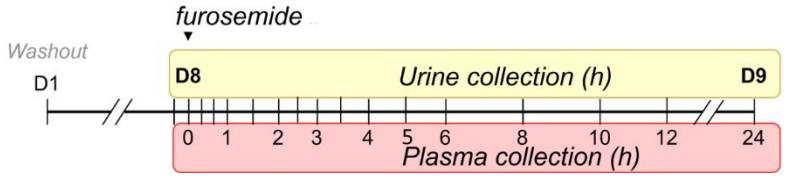
3.1. *Part 1 Arm A*



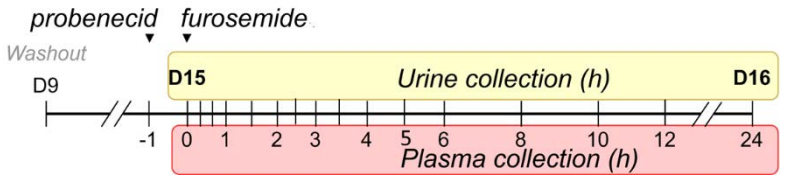
3.2. *Part 1 Arm B*



3.3. *Part 2 Arm A*



3.4. *Part 2 Arm B*



Study days. Subjects will be asked to present to the clinical research space in the Health Sciences Building or Nursing Building on the morning of each 14-hour inpatient visit. Vital signs will be checked and recorded on case forms. Subjects will be asked of any change to their health status; responses will be recorded on case forms. An intravenous line will be placed in one arm, and a blood sample (5 mL) will be drawn through the intravenous line. Subjects will then be administered a single dose of the object drug (metformin or furosemide) (Arm A) or the inhibitor drug (cimetidine or probenecid) followed one hour later by the object drug (Arm B). During all Arms, blood will be drawn from the intravenous line 0.5 hours before and 0.33, 0.67, 1, 1.5, 2, 2.5, 3, 3.5,4, 5, 6, 8, 10, 12, and 24 after object drug administration. Urine will be collected into multiple jugs from 0-24 hours. Subjects will be given a urine jug to take home and void into until they return to the clinical research space for the blood draw 24 hours after object drug administration. After the 12-hour blood draw of all Arms, subjects will be allowed to leave once deemed safe by the study coordinator.

All Arms will be separated by at least 7 days to ensure sufficient washout of all study drugs; probenecid has the longest average half-life (~6 hours), thus all drugs should be eliminated within 2-3 days. Subjects will be asked to refrain from consuming any dietary/herbal supplements or citrus juices for at least 1 week prior to each 14-hour inpatient visit and for the duration of the study. They will be asked to refrain from alcoholic and caffeinated beverages the evening before and the morning of each inpatient and outpatient visit.

Study drug acquisition. Dr. John White, a longstanding collaborator/co-investigator and registered pharmacist in WA, will oversee the acquisition and storage of metformin, cimetidine, furosemide, and probenecid.

Pharmacokinetic and statistical analysis. Plasma and urine samples will be analyzed for the study drugs and endogenous transporter substrates by UPLC/MS/MS. The pharmacokinetics of each analyte will be determined using traditional noncompartmental analysis methods and the pharmacokinetics analysis software, Phoenix WinNonlin™ (v8.3, Certara, Princeton, NJ). The primary analysis will test overall differences in the C_{max}, $AUC_{0\text{-}24h}$, and renal clearance (Cl_R) of furosemide, metformin, and all detected endogenous substrates between the control (object drug only) and treatment (inhibitor + object drug) groups. C_{max} will be obtained directly from the plasma concentration-time profiles, and $AUC_{0\text{-}24h}$ will be calculated using the linear up-log down trapezoidal method. Cl_R will be calculated as the ratio of $X_{e,0\text{-}24h}$ to $AUC_{0\text{-}24h}$, where X_e denotes the cumulative amount of drug/endogenous substrate excreted into the urine. C_{max}, $AUC_{0\text{-}24h}$, $X_{e,0\text{-}24h}$, and Cl_R (with and without inhibitor) will be compared using the paired Student's *t*-test or Wilcoxon test (depending on the data distribution). If an endogenous substrate is only detected in either blood or urine sample, the $AUC_{0\text{-}24h}$ or $X_{e,0\text{-}24h}$ of the drug will be compared with the corresponding metrics of the endogenous substrates.