TITLE OF THE STUDY: Impact of Metformin and Polysorbate 80 on Drug Absorption and Disposition

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PROTOCOL SUMMARY

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PHASE: Phase 4

METHODOLOGY: This is an open-label, randomized, single-dose, placebo-controlled, fasted, crossover pharmacokinetic study (and not a treatment study) of the impacts of metformin and polysorbate 80 in n=12 healthy volunteers. All volunteers receive metformin, polysorbate 80, and placebo. In the metformin arm, metformin will be administered for about 6 days to potentially repress bile salt export pump (BSEP). On about day 7, a single dose of several drugs (i.e., a cassette dose, composed of pravastatin, chenodiol, valacyclovir, and enalaprilat) is administered, and the pharmacokinetic profiles of pravastatin and chenodiol will be quantified. In the polysorbate 80 arm, polysorbate 80 will be administered for about 6 days to potentially inhibit intestinal PepT1 and ASBT. On about day 7, the single cassette dose along with polysorbate 80 is administered, and the pharmacokinetic profiles of acyclovir, chenodiol, and enalaprilat will be quantified. In the placebo arm, placebo will be administered for about 6 days. On about day 7, the single cassette dose is administered, and the pharmacokinetic profiles of pravastatin, chenodiol, acyclovir, and enalaprilat will be quantified.

STUDY CENTER: University of Maryland

NUMBER OF SUBJECTS: at least n=12

STUDY OBJECTIVES: The study employs two-sub-studies that share a common placebo arm. The objective of one sub-study is to assess the impact of metformin on pravastatin and chenodeoxycholic acid pharmacokinetics. We hypothesize that metformin represses the bile salt export pump (BSEP) in the liver, which excretes pravastatin and chenodeoxycholic acid from the liver into the bile. The objective of the other sub-study is to assess the impact of polysorbate 80 on valacyclovir, chenodeoxycholic acid, and enalaprilat pharmacokinetics. We hypothesize that polysorbate 80 inhibits uptake transporters in the intestine, which absorb valacyclovir and chenodeoxycholic acid in the gut via the peptide transporter 1 (PepT1) and apical sodium–bile acid transporter (ASBT), respectively. Enalaprilat is passively absorbed but with low permeability, and thus serves as a passive absorption reference. Primary outcomes in the one sub-study are pravastatin and chenodeoxycholic acid AUC and Cmax pharmacokinetics, compared to placebo. Primary outcomes in the other sub-study are acyclovir, chenodeoxycholic acid, and enalaprilat AUC and Cmax pharmacokinetics, compared to placebo. Valacyclovir is converted to acyclovir after valacyclovir is absorbed. Secondary measures are AUC and Cmax of endogenous bile acids.

Impact of Metformin and Polysorbate 80 on Drug Absorption and Disposition

Lay Summary

A tablet is composed of a drug and so-called inert ingredients or excipients (e.g., fillers, binders). For a drug to be effective after oral dosing, it must be absorbed across cell membranes and reach its site of action. For some drugs, drug movement across cell membranes relies upon membrane-bound transporters or carriers, which normally help nutrients be absorbed and distributed throughout the body. Administration of certain drugs and excipients may reduce or inhibit these transporters, possibly reducing how other drugs are absorbed and distributed. The drug metformin (to treat diabetes) will be administered to healthy volunteers to see if it impacts the transport of the drugs pravastatin and chenodiol (chenodeoxycholic acid). The excipient polysorbate 80 (a surfactant) will be administered to healthy volunteers to see if it impacts the transport of the drugs valacyclovir, chenodiol, and enalaprilat. All the drugs (i.e., metformin, pravastatin, chenodiol, valacyclovir, and enalaprilat) and excipients (i.e., polysorbate 80) in this study are FDA-approved and used here at a lower amount than allowed.

Background

This study concerns potential drug-drug and drug-excipient interactions that are mediated by drug transporters. The study employs two-sub-studies that share a common placebo arm.

Regarding the metformin arm, we have recently shown that metformin represses BSEP expression in human primary hepatocytes. Pravastatin and chenodeoxycholic acid (chenodiol) are substrates for BSEP. BSEP function is not well studied in humans. In general, gene repression by drugs is not well studied in humans (e.g., unlike gene induction or enzyme inhibition). It has not been reported that metformin modulates BSEP.

Regarding the polysorbate 80 arm, many medications are in use for decades after phase 3 studies. In the life-cycle of such medications, medication manufacture is frequently altered (e.g., move to larger manufacturing scale or different location, change in excipients). Also, availability of generics further broadens the diversity of excipients that are used. We have previously shown that the most common excipients had no impact of the pharmacokinetics of so-called BCS class 3 drugs. This finding resulted in greater regulatory relief (i.e. use of in vitro studies rather than human pharmacokinetic studies) in assuring on-going drug product

bioequivalence. A limitation of this regulatory relief is that such relief is not granted to drugs that that may be absorbed via a transporter, given the general potential concern that an excipient can modulate transporter-mediated drug absorption. The second sub-study addresses this potential concern. Polysorbate 80 is a surfactant that has been shown to inhibit transporters in vitro. Corresponding studies of polysorbate 80 in humans have not been performed.

Procedures

In this non-treatment, pharmacokinetic study. There will be a screening visit and three pharmacokinetic arms/rounds/interventions (i.e., metformin, polysorbate 80, and placebo). For each arm, individual subjects willr eceive twice daily doses of the intervention (i.e., bid) for about 6 consecutive days at home, followed by a 10-hour pharmacokinetic visit at GCRC. There are five visits in total: screening visit, round 1 intervention pick up, and three 10-hour pharmacokinetic visits on about day 7 (i.e., one for each intervention) involving administration of a cassette dose (as well as pick up of intervention for next arm). The cassette dose is the co-administration of pravastatin, chenodiol, valacyclovir, and enalaprilat. Polysorbate 80 is also included in the cassette dose in the polysorbate 80 arm. Blood from each arm (i.e., last sample at 10 hr) will be collected at each pharmacokinetic visit. Participants are healthy volunteers.

Each subject who completes the study will have taken placebo, metformin, and polysorbate 80. We aim to complete 12 subjects. Replacement of dropouts is allowed.

Subjects who have successfully screened (i.e., met all I/E criteria) will be randomized into one of six sequences. The 6 sequences are as follows: Sequence A will receive drugs in the following order: placebo, metformin, polysorbate 80. Sequence B will receive drugs in the following order: metformin, polysorbate 80, placebo. Sequence C will receive drugs in the following order: polysorbate 80, placebo, metformin. Sequence D will receive drugs in the following order: polysorbate 80, metformin, placebo. Sequence E will receive drugs in the following order: placebo, polysorbate 80, metformin. Sequence F will receive drugs in the following order: metformin, placebo, polysorbate 80. Randomization is to a sequence A, B, C, D, E, or F. All subject data will be de-identified.

The dose of metformin is 500 mg bid. The dose of polysorbate 80 is 400 mg bid. For the metformin and placebo arms, the single cassette dose are four probe compounds: 80 mg pravastatin, 250 mg chenodiol, 500 mg valacyclovir, and 20 mg enalaprilat. In the polysorbate 80 arm, 400 mg polysorbate 80 as an additional (i.e., fifth) component of the cassette dose of probe compounds. Screening and all drug study visits will be conducted in the GCRC.

Screening (Visit 1): At this visit, the HIPAA and consent forms will be signed and dated. A physical exam with a medical/medication history will be conducted. Clinical safety labs will be performed. Female subjects will be asked if they are breast feeding, trying to become pregnant, or are pregnant. Female subjects of child-bearing potential will have a urine pregnancy test. Subjects will be asked if they are taking any drug that may affect plasma concentrations of metformin, pravastatin, chenodiol, valacyclovir, or enalaprilat; or drugs that are modulated by any of them. Also, prior to the metformin arm, subjects will be asked if they are taking any drug that may affect plasma concentrations of metformin or drugs that are modulated by metformin.

Round 1 intervention pick up (Visit 2): The subject will pick up either metformin, polysorbate 80, or placebo for the first intervention arm. A urine pregnancy test will be done for a woman of child bearing potential. The intervention dose is metformin 500 mg bid, polysorbate 80 400mg bid, or one placebo tablet bid for 6 days, with a 10-hour pharmacokinetic visit on day 7. The intent is to achieve bid dosing of intervention each and every day until the10-hour pharmacokinetic visit on about day 7.

First Pharmacokinetic Study Arm Visit (Visit 3): Subjects are requested to arrive on about day 7 of the first study arm at the GCRC by approximately 6 am for preparation for the study, after an overnight fast of 10 hours prior to cassette dosing, and remain fasted for an additional 4 hours. Women of child-bearing potential will take a urine pregnancy test. If inclusion/exclusion requirements are met, preferably, an IV catheter is inserted for drawing blood.

A single cassette dose of four probe compounds will be orally co-administered: 80 mg pravastatin tablet, 250 mg chenodiol tablet, 500 mg valacyclovir tablet, and 20 mg enalaprilat solution. In the polysorbate 80 arm, 400 mg polysorbate 80 (liquid) will also be orally administered in the cassette dose of probe compounds. The cassette dose will be orally administered with 240 ml of water at approximately 7 am. Pharmacokinetic (PK) blood levels will be drawn at the scheduled times: prior to drug administration, then after drug administration at 0.5, 1, 1.5, 2, 3, 4, 6, 8, and 10 hr post-dose.

Four hours after taking cassette dose (approximately 11 am), a lunch will be served. While in the GCRC, subjects will fast between meals except for water. However, no water is allowed 1 hour before and after drug administration. A snack will be served 7.5 hours after taking cassette dose (approximately 2:30 pm).

All pharmacokinetic blood samples (4-7cc) will be collected in a heparinized green top tube, placed on ice immediately, centrifuged (>2000 rpm at +4 degrees for 10 min) within 15 minutes of collection to produce plasma, split into two or more plasma aliquots then frozen at -20 or -80 degrees C, until transferred for pharmacokinetic quantification. Hepatic function testing will be

performed from an additional 5 cc blood sample, taken at the subject's last sampling of the metformin arm, to consider potential hepatotoxicity. The subject will pick up either metformin, polysorbate 80, or placebo for the second interventional arm.

Second and Third Pharmacokinetic Study Arm Visits (Visits 4 and 5): Procedures are the same as above in first pharmacokinetic study arm, per randomized sequence, in this full crossover study.

INCLUSION CRITERIA:

1. Subject is healthy, as determined by screening evaluation that is not greater than 60 days before the first study visit.

2. Subject is male or female between 18 and 65 years of age, inclusive.

3. Subject is an acceptable candidate for venipuncture.

4. Subject is willing to stop all non-routine OTC medications, as well as vitamins, dietary supplements, and herbals, for 24 hours prior to study drug administration and during pharmacokinetic study visits

EXCLUSION CRITERIA:

1. Subject has a significant medical disease (including cardiovascular, pulmonary, hematologic, endocrine, immunologic, neurologic, renal, gastrointestinal, metabolic, or psychiatric).

2. Subject has a clinically significant history or presence of any clinically significant gastrointestinal pathology (e.g. chronic diarrhea, inflammatory bowel diseases), unresolved gastrointestinal symptoms (e.g. diarrhea, vomiting), liver or kidney disease, or other conditions known to interfere with the absorption, distribution, metabolism or excretion of study drugs.

3. Subject has a history of liver or gallbladder disease, or history of myopathy

4. Subject has a history of angioedema either with or without previous treatment with an angiotensin converting enzyme inhibitor.

5. Subject was previously diagnosed with diabetes, or treated with antidiabetic agents

6. Subject has a history of alcohol or drug abuse, which in the opinion of the PI or medical physician, could jeopardize the subject's health or would compromise the subject's ability to participate in this trial.

7. Subject is pregnant, breast feeding, or trying to become pregnant.

8. Female subject of childbearing potential is unwilling or unable to use a medically acceptable method of contraception throughout the entire study period and for one week after the study is completed. Medically acceptable methods of contraception that may be used by the subject and/or her partner are: oral birth control pill, condom with spermicide, diaphragm with spermicide, IUD, vaginal spermicidal suppository, surgical sterilization of patient or their partner(s), abstinence, or hormonal-based patches, ring, injections, and implants.

9. Subject routinely uses (i.e. daily or weekly) prescription medication except hormonal birth control medication, routinely uses (i.e. daily or weekly) OTC medication, or routinely uses niacin to treat hypercholesterolemia. OTC medications do not include vitamins, dietary supplements, or herbals.

10. Subject routinely uses (i.e. daily or weekly) acid blockers, antacids, anti-diarrhea, stimulants, appetite suppressants, or anti-nausea medication or other drugs that modulate GI function.

11. Subject is currently taking metformin, valacyclovir, acyclovir, chenodiol, pravastatin, enalapril, enalaprilat, or medications known to interact with any of these medications.

12. Subject has a history or allergy or sensitivity to metformin, valacyclovir, acyclovir, chenodiol, pravastatin, polysorbate 80, enalapril, enalaprilat, or history of any drug hypersensitivity or intolerance which, in the opinion of the PI or medical physician, would compromise the safety of the subject or the study.

13. Subject has liver impairment as assessed by alanine aminotransferase (ALT), aspartate aminotransferase (AST), or total bilirubin levels greater than the upper limit of normal (ULN).

14. Subject has renal impairment as assessed by creatinine clearance lower than 60mL/min/1.73m2, using the CKDEPI formula.

15. Subject is not willing or able to be adherent to study protocol (e.g., study visits).

16. Subject has a condition in which in the opinion of the PI or medical physician would increase risk to the subject or interfere with the integrity of the study.

Monitoring Plan

Data Safety Monitoring will be performed by a physician who is not on the study team. In closed review of subjects (i.e. de-identified data), the physician will review the following information: AEs (recorded on a flow sheet), screen failures, subject withdraws and terminations, and enrollment. Reviewed data will include clinical summaries, enrollment

numbers, and adverse events. Additionally, she will conduct such reviews after the completion of the first four subjects, and then quarterly.

Statistical Analysis Plan

The study employs two-sub-studies that share a common placebo arm. The objective of one sub-study is to assess the impact of metformin on pravastatin and chenodeoxycholic acid pharmacokinetics. We hypothesize that metformin represses the bile salt export pump (BSEP) in the liver, which excretes pravastatin and chenodeoxycholic acid from the liver into the bile. Enalaprilat is passively absorbed but with low permeability, and thus serves as a passive absorption reference. Primary outcomes in this sub-study are pravastatin and chenodeoxycholic acid AUC and Cmax pharmacokinetics (0-10 hr), compared to placebo. Values for chenodeoxycholic acid are base-line corrected, where baseline-corrected chenodeoxycholic acid is chenodeoxycholic acid concentration minus chenodeoxycholic acid concentration value at time zero (i.e. t=0). A one-sided t-test will be used to assess if pravastatin AUC and pravastatin Cmax are larger with metformin than without metformin (i.e. compared to placebo). A one-sided t-test will be used to assess if chenodeoxycholic acid AUC and chenodeoxycholic acid Cmax are reduced with metformin than without metformin (i.e. compared to placebo). Assessment for either larger or reduced impacts reflects the potential differential pharmacokinetic handling by BSEP.

The objective of the other sub-study is to assess the impact of polysorbate 80 on valacyclovir, chenodeoxycholic acid, and enalaprilat pharmacokinetics. We hypothesize that polysorbate 80 inhibits uptake transporters in the intestine, which absorb valacyclovir and chenodeoxycholic acid in the gut via the peptide transporter 1 (PepT1) and apical sodium–bile acid transporter (ASBT), respectively. Primary outcomes in this sub-study are acyclovir, chenodeoxycholic acid, and enalaprilat AUC and Cmax pharmacokinetics (0-10 hr), compared to placebo. Valacyclovir is converted to acyclovir after valacyclovir is absorbed. Values for chenodeoxycholic acid are base-line corrected, where baseline-corrected chenodeoxycholic acid is chenodeoxycholic acid concentration minus chenodeoxycholic acid concentration value at time zero (i.e. t=0). A one-sided t-test will be used to assess if acyclovir AUC, acyclovir Cmax, chenodeoxycholic acid AUC, and chenodeoxycholic acid Cmax are reduced with polysorbate 80 than without polysorbate 80 (i.e. compared to placebo). A one-sided t-test will be used to assess if enalaprilat AUC and enalaprilat Cmax are larger with polysorbate 80 than without polysorbate 80 (i.e. compared to placebo). Assessment for either larger or reduced impacts reflect the differential pharmacokinetic absorption mechanisms, and hence potential impact of polysorbate 80.

In each sub-study, secondary measures are AUC and Cmax of endogenous bile acids (i.e. cholic acid, deoxycholic acid, chenodeoxycholic acid, lithocholic acid, ursodeoxycholic acid; and their glycol- and tauro-conjugates) [0-10 hr]. A one-sided t-test will be used to assess if each bile acid AUC and Cmax are reduced with metformin than without metformin (i.e. compared to placebo). A one-sided t-test will be used to assess if each bile acid AUC and Cmax are larger with polysorbate 80 than without polysorbate 80 (i.e. compared to placebo).