TITLE OF THE STUDY: Prediction of Itraconazole Oral Absorption From In Vitro Dissolution

ClinicalTrials.gov ID: NCT04035187

Document date: June 11, 2019

Abbreviated title: Itraconazole Oral Absorption

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PROTOCOL SUMMARY

TITLE OF THE STUDY: Prediction of Itraconazole Oral Absorption From In Vitro Dissolution

PHASE: Phase 4

METHODOLOGY: Randomized, open-label, 4-way, cross-over, four period, fasted single-dose study comparing pharmacokinetic area-under-the-curve (AUC) of fast tablet, medium tablet, and slow tablet.

STUDY CENTER: University of Maryland

NUMBER OF SUBJECTS: at least n=12

STUDY OBJECTIVES: The primary outcome will be the assessment of pharmacokinetic area-under-the-curve (AUC) of fast tablet, medium tablet, and slow tablet, with regard to rank-order of point estimates, after a single oral dose of itraconazole in at least n=12 healthy volunteers. It is hypothesized that fast dissolving tablet will provide the highest AUC point estimate value, and the slow dissolving tablet will provide the lowest AUC point estimate value.

Prediction of Itraconazole Oral Absorption From In Vitro Dissolution

Lay Summary

For tablets to be absorbed, the drug must dissolve after being swallowed. Drugs with low solubility sometimes require the inert ingredients in tablets to help the drug dissolve after being swallowed. This study uses itraconazole as an example drug with low solubility. Itraconazole tablets with different inert ingredients and manufacturing will be administered to healthy volunteers to see if the different inert ingredients and manufacturing impact drug absorption.

Background

Itraconazole is an example drug with low solubility, where the rate of drug dissolution will impact the amount of drug that is absorbed. A measure of the amount of drug that is absorbed is pharmacokinetic area-under-the-curve (AUC). It is hypothesized that fast dissolving tablet will provide the highest AUC point estimate value, and the slow dissolving tablet will provide the lowest AUC point estimate value.

Procedures

In this non-treatment, pharmacokinetic study. There will be a screening visit and four pharmacokinetic study arms for all enrolled subjects. Subjects will be enrolled on an ongoing basis until either the anticipated number of required subjects for at least n=12 completed subjects is achieved. In each pharmacokinetic study visit occasion, individual subjects will receive a single dose of one (and only one) of four drug products. The products are fast tablet, medium tablet, slow tablet, and commercial oral solution.

Subjects will be randomized into one of four sequences, A, B, C, or D. Sequence A will receive drug products in the following order: 1, 2, 4, 3. Sequence B will receive drug products in the following order: 2, 3, 1, 4. Sequence C will receive drug products in the following order: 3, 4, 2, 1. Sequence D will receive drug products in the following order: 4, 1, 3, 2. Numbers 1, 2, 3, 4, are Fast tablet, Medium tablet, Slow tablet ,and oral solution, respectively.

Each tablet contains itraconazole 100mg, which is sub-clinical in amount. The dose of commercial oral solution (10mg/ml) is also itraconazole 100mg. In each period, blood samples will be collected 0-48 h. Additionally, for oral solution, a blood samples will be collected at 72.0 hr post-dose.

Screening: At this visit, the HIPAA and consent forms will be reviewed with the subject by a member of the research staff; they will be signed and dated. Consenting will also discuss and provide a payment plan. Demographic information will be obtained. A brief physical exam with a medical/medication history, including smoking and alcohol, will be conducted. ECG will be performed. Clinical safety labs at screening include hepatic and renal function tests (i.e.creatinine, AST, ALT, and total bilirubin), and hemoglobin to test for anemia. 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. The subject will be asked about willingness to avoid caffeine products for 24 hours before and day of study visit. The subject will be asked about willingness to stop Over-the-Counter (OTC) drugs for 24 hours before and days of study visits. The subject will be asked if willing, for each of the four drug study periods, to stop consuming grapefruit, grapefruit products, star fruit, star fruit products, Seville oranges, or St. John's wort from 72-hour before study drug administration until the period's last blood sample. The subject will be asked if willing to fast during the study visits except for meals supplied in the study. If subject meets all eligibility requirements, then appointments are scheduled for the drug study visits. The first study visit will be within 30 days of the screening visit.

Drug/Pharmacokinetic Study Visits: Subjects will be requested to arrive by approximately 7am on study visit, after an overnight fast of 10 hours prior to taking test drug, and remain fasted for an additional 4 hours. Women of child-bearing potential will take a urine pregnancy test.

Drug (i.e. a single tablet or 10ml of oral solution) will be orally administered with 240ml of clear, non-bottled water at approximately 8am. All drugs will be stored and dispensed by the UMMC investigational drug pharmacy. Pharmacokinetic (PK) blood levels will be drawn at the schedule times: prior to drug administration, then after drug administration at 1.0, 2.0, 3.0, 4.0, 5.0, 6.0, 8.0, 12.0, 15.0, 24.0, 36.0, and 48.0 hr post-dose. Additionally, for oral solution, a blood samples will be collected at 72.0 hr post-dose.

Standardized meals and snacks will be served during each PK study arm. Meals and snacks include beverages. Four hours after taking test drug, or approximately noon, a lunch will be served. Lunch beverage will only include clear, non-bottled water. Lunch will exclude beverage with low pH (e.g. soft drinks, fruit juices, sport and energy drinks, tea, coffee). An afternoon snack will be served 3 hours later, or at approximately 3pm. Dinner will be served 3 hours later or at approximately 6pm. An evening snack will be served 3 hours later, or at approximately

9pm. While in the GCRC, subjects will fast between meals or snacks except for clear, non-bottled water. However, no water is allowed 1 hour before and after drug administration. There are 4 visits for each tablet arm (i.e. a second, third, and fourth visit of the arm for the 24, 36, and 48 hr blood draws, respectively). There are 5 visits for the oral solution arm (i.e. a second, third, fourth, and fifth visit of the arm for the 24, 36, 48, and 72 hr blood draws, respectively). Subjects will return for the next study arm, preferably 1 week later with a minimum of a wash out of 7 days and no more than 60 days.

Subjects will be monitored for AEs during study days. At each study visit, subjects will be asked about any AE that may have occurred between study visits. At the last study visit, an additional 5 cc (1 teaspoon) will be collected for liver function test safety labs. All AE will be documented in the source documents by research personnel. AEs and SAEs will be reported per UMB HRPO guidelines.

INCLUSION CRITERIA:

1. Subject is healthy, as determined by screening evaluation that is not greater than 30 days before the first drugs tudy 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.

5. Subject is willing, for each of the four drug study periods, to stop consuming grapefruit, grapefruit products, starfruit, star fruit products, Seville oranges, and St. John's wort from 72-hour before study drug administration until the period's last blood sample.

6. Subject is willing to not smoke (or use e-cigarettes) during study visits.

EXCLUSION CRITERIA:

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

2. Subject shows evidence of congestive heart failure or history of congestive heart failure.

3. Subject exhibits electrocardiogram (12 lead) with clinically significant abnormalities (e.g. QTcF >450 msec).

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

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

6. 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.

7. 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 (i.e. daily or weekly) St. John's Wort. OTC medications do not include vitamins, dietary supplements, or herbals.

8. 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.

9. Subject is currently taking itraconazole or medication known to interact with itraconazole.

10. Subject is allergic to itraconazole.

11. 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).

12. Subject has renal impairment as assessed by creatinine clearance lower than 50mL/min/1.73m2, using the CKD-EPI formula.

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

14. 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.

15. Subject has received an investigational product within 30 days prior to study drug administration, plans to receive an investigational product during their study participation period, or plans to donate blood to any other clinical trial during their study participation period.

16. Subject has provided plasma donation within 1 month of screening or any blood donation/loss more than 500 mL within 8 weeks prior to study drug administration.

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

This is a pharmacokinetic, in vitro-in vivo correlation study. The primary outcome will be the assessment of pharmacokinetic area-under-the-curve (AUC) of fast tablet, medium tablet, and slow tablet, with regard to rank-order of point estimates, after a single oral dose of itraconazole in at least n=12 healthy volunteers. It is hypothesized that fast dissolving tablet will provide the highest AUC point estimate value, and the slow dissolving tablet will provide the lowest AUC point estimate value. The point estimate is the simple mean value. There will either be a rank-order correlation or not.