Form A

IRB #	STU-2023-1257

PROTOCOL FORM / RESEARCH DESCRIPTION

If an item does not apply to your research project, indicate that the question is "**not applicable**" – do not leave sections blank

Click once on the highlighted entry in each box to provide your response. Click the item number/letter or word, if hyperlinked, for detailed instructions for that question. If your response requires inserting a table, picture, etc, you may need to first delete the box that surrounds the answer and then insert your table or other special document.

1. Purpose and objectives. *List the purpose and objectives:*

This pilot study will determine whether the drug Tenapanor reduces urine oxalate excretion in normal, healthy subjects receiving a standardized high-oxalate diet.

Hypothesis: Tenapanor limits the absorption of dietary oxalate and reduces urinary oxalate excretion.

2. Background.

- Describe past experimental and/or clinical findings leading to the formulation of your study.
- For research involving investigational drugs, describe the previously conducted animal and human studies.
- For research that involves FDA approved drugs or devices, describe the FDA approved uses of this drug/device in relation to your protocol.
- Attach a copy of the approved labeling as a product package insert or from the Physician's Desk Reference.

You may reference sponsor's full protocol or grant application (section number and/or title) or if none, ensure background includes references.

Please respond to all components of this item, or clearly indicate which components are not applicable.

a. Background

The prevalence of kidney stones is increasing in the United States where over two-thirds of kidney stones are primarily composed of calcium oxalate. One of the main risk factors for calcium oxalate formation is elevated urine oxalate (hyperoxaluria). Many cases of hyperoxaluria are to excess absorption of dietary oxalate associated with gastrointestinal disease and/or surgery. There are no currently available therapies and treatment options are mostly confined to management through dietary manipulations, which are not always feasible or effective. We are proposing to test whether the FDA-approved drug Tenapanor will block intestinal oxalate absorption.

Tenapanor was designed as a non-absorbable inhibitor of the intestinal sodium/proton exchanger known as NHE3 (encoded by gene SLC9A3) which is responsible for sodium and water absorption. In 2019, it was approved for the treatment of constipation associated with irritable bowel syndrome (IBS-C) and marketed as Ibsrela – copy of product approval package and insert attached. Pre-clinical studies also discovered Tenapanor blocks phosphate absorption by the intestine and in October 2023 it was approved for treating hyperphosphatemia in patients with chronic kidney disease (CKD) and sold as Xphozah – copy of product approval letter and insert attached.

Since phosphate and oxalate are passively absorbed from the intestine by the same pathway, we are proposing to perform a proof-of-concept study that will test the hypothesis that Tenapanor limits the absorption of dietary oxalate by the intestine and reduces urinary oxalate excretion.

b. Current practice

Hyperoxaluric stone-formers are counseled to reduce or avoid the consumption of oxalate-rich foods and/or increase calcium intake (calcium binds with oxalate in the gut and helps limit its absorption). Patients with fat malabsorption and steatorrhea can also benefit from a low-fat diet. If relevant and feasible, treatment of the underlying GI disorder may help resolve hyperoxaluria.

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3. Study Design.
Describe the study design (e.g., single/double blind, parallel, crossover, etc.) Consider inserting a scheme to visually present the study design.

Randomized, single-blind, placebo-controlled, two-phase, crossover study with 10 healthy adult volunteers.

4. Research Plan / Description of the Research Methods:

4.a. Provide a **comprehensive narrative** describing the **research methods**.

1) Provide the **order in which tests/procedures will be performed**,
2) Provide the **setting** for these events and a description of the **methods used to protect privacy** during the study.
3) Provide the **plan for data analysis** (include as applicable the **sample size calculation)**

Please respond to all components of this item, or clearly indicate which components are not applicable.

Study Design

Screening – One 24-hour urine for analysis of stone-risk profile, one blood sample for comprehensive metabolic panel, and cystatin C, one stool sample for fecal calprotectin, physical exam, social and medical history, vital signs, demographic information, personal information.

Recruitment – 10 normal, healthy adult volunteers identified from personal contacts/department team members.

This is a two-phase study, each phase in 5 days in duration.

Phase 1: The subjects will consume a frozen oxalate-rich metabolic diet for 5 days while taking 50 mg Tenapanor or Placebo twice a day just prior to the morning and evening meals. On days 4 and 5 they will collect two 24-hour urines for measurement of urine oxalate and stone-risk profile.

Washout: The subjects will undergo a 9-day washout period.

Phase 2: The subjects will consume a frozen oxalate-rich metabolic diet for 5 days while taking 50 mg Tenapanor or Placebo twice a day just prior to the morning and evening meals. On days 4 and 5 they will collect two 24-hour urines for measurement of urine oxalate and stone-risk profile.

Analysis

The analysis will compare the effects on urine biochemistry (including oxalate, phosphate, sodium, pH) between Tenapanor and Placebo using a two-sided t test.

The data from this proof-of-concept pilot study with 10 healthy volunteers will be used to determine whether Tenapanor is worthy of further study for reducing urine oxalate excretion.

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4.b. List of the study intervention(s) being tested or evaluated under this protocol

☐ **N/A -** this study does not test or evaluate an intervention. Skip to item 4.d.

#	Study intervention(s) being tested or evaluated under the protocol *Add or delete rows as needed*	Affiliate Place a check next to institution(s) where the intervention will be performed	Local Standard Practice? Indicate whether the intervention is considered acceptable practice locally for applicable institutions
1	Tenapanor	☒ UTSW	☐ Yes
		☐ PHHS	☐ Yes
		☐CMC	☐ Yes
		☐THR	☐ Yes
		☐TSRH	☐ Yes
		☐ Other: _____	☐ Yes

4.c. Risk:Benefit Analysis of study interventions being tested or evaluated under this protocol

For each study intervention identified in section 6b above, complete a risk:benefit analysis table.

(Two tables are provided, copy & paste additional tables as needed or delete both tables if this study does not test an intervention)

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4.c. **Study Intervention #1** Tenapanor	
List each group exposed to this intervention on a separate line. (e.g., experimental, control, Arm A, Arm B, etc) **Or** state All Groups/Subjects	For each group, list the **benefits** of this intervention. (Benefits can be directly from the intervention or from a monitoring procedure likely to contribute to the subject's well being). If there are no benefits, state "none".
Normal, healthy subjects	Lower urine oxalate

If you are requesting a Waiver of Informed Consent, complete the table below.

If you have a consent form, **list the reasonably foreseeable risks in the consent form (and do not complete this section).**

List the risks according to the probability (likely, less likely or rare) and magnitude (serious or not serious).
(include: 1) expected adverse events; 2) rare and serious adverse events; 3) all other psychological, social, legal harms)
Do not delete frequency. Frequency must be estimated because it will assist you with determining which adverse events will require prompt reporting.

	Not serious	**Serious**
Likely These risks are expected to occur in more than **20** out of **100** subjects.	•	•
	Not serious	**Serious**
Less likely These risks are expected to occur in **5-20** subjects or less out of **100** subjects.	•	•
		Serious
Rare These risks are expected to occur in less than **5** subjects out of **100**		•

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4.d. List ALL other research procedures or components not listed in table 4.b.
The combination of Tables 4b and 4d should account for all of the research procedures that will take place during this study.

Consider grouping similar procedures under a single component (e.g., blood work, CT = safety assessments)

#	Research component • **individual procedures** *example:* **Eligibility Assessments** • History and physical • Questionnaire • Laboratory tests *Add or delete rows as needed*	**Column A** **Local Standard Practice** Indicate the number of times each procedure will be performed as stipulated in the research plan **that would be performed if the participant were not participating in the study.**	**Column B** **Research Only** Indicate the number of times each procedure will be performed solely for research purposes *(meaning that the participant would not undergo the same number of procedures or would not undergo the procedure(s) at the same frequency if they were not participating in the study)*	**Column D** **Risks** **If you are requesting a Waiver of Informed Consent, complete the table below.** List the reasonably expected risks for each procedure or group of procedures under the following categories as appropriate: • Serious and likely; • Serious and less likely; • Serious and rare; • Not serious and likely; • Not serious and less likely
1	**Eligibility Assessments**			
	History and physical	**0**	**1**	
	Questionnaire	**0**	**1**	
2	**Urine and blood work**			
	24-hour urine collection	**0**	**5**	
	Blood draw	**0**	**1**	
	Stool sample	**0**	**1**	

5. Safety Precautions. *(Describe safeguards to address the serious risks listed above.)*

a. Describe the procedures for protecting against or minimizing any potential risks for each of the more than minimal risk research procedures listed above.

n/a

b. Where appropriate, discuss provisions for ensuring necessary medical or professional intervention in the event of adverse events, or unanticipated problems involving subjects.

Participants will be advised at study entry of the nature of potential risks and side effects. Those with increased risk of injury will be excluded from the study. If symptoms appear patients will be asked to contact the investigators. Pending the results of the evaluation, the investigator may discontinue the study. An additional potential risk is loss of privacy. Study participants have a right to privacy and all information that is obtained in connection with this study that can be identified with the participant will not be released to anyone other than the investigators. The results of the study may be published in scientific journals without identifying the participants by name. Records of subject participation may be reviewed by the Institutional Review Board.

Participant safety will be monitored to ensure that all study-related procedures are being well tolerated. Participant safety will be monitored by the PIs and any unexpected and serious adverse events reported to the IRB per local regulation. The validity and integrity of the study data will be closely monitored by the biostatistician. The Research Personnel and PIs will meet weekly to review and discuss patient safety, study data quality and timeliness, participant recruitment, accrual and retention, participant risk versus benefit, protocol adherence and other factors that affect study outcome.

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c. Will the safeguards be different between/among groups?	
☐ Yes	☑ No
If yes, describe here	