Treatment of acute renal failure in patients with decompensated cirrhosis with pentoxyfylline: A placebo controlled, blinded pilot study

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Brief Study Synopsis

Study Phase: Pilot

Primary hypothesis: Pentoxyfylline (PTX) therapy at 1200 mg per day or the renally dose equivalent in addition to standard of care is superior to placebo in the treatment of acute renal failure (ARF) not responsive to volume resuscitation in hospitalized patients with cirrhosis.

Study design: Prospective, placebo-controlled, randomized pilot trial.

Each hospitalized subject will undergo pre-dosing screening with review of his or her history and physical exam from the day of enrollment and safety assessment to ensure no contraindication to use of PTX.

ARF will be defined according to the definition put forth by and validated prospectively by collaboration between the International Ascites Club (IAC) and the Acute Dialysis Quality Initiative as a rise in creatinine of 0.3 mg/dl or 50% from baseline creatinine, which will be defined as the most recent stable measurement before admission.[1]

Baseline testing will be obtained from hospitalization records, including but not limited to chemistry panel, liver function testing, urinalysis, urine electrolytes, coagulation studies, blood cultures, chest x-ray, diagnostic paracentesis, abdominal ultrasound with Doppler.

Subjects will take either placebo three times a day or PTX 400mg three times a day or 400mg twice a day for eGFR 10-50 and 400mg once a day for eGFR <10 for 14 days in addition to standard inpatient care. Treatment will be continued for 14 days unless a study endpoint has been reached at which time either PTX or placebo will be stopped.

Total study subjects expected: 30 patients with cirrhosis hospitalized ARF

Duration of study: 180 days

Study Drugs: PTX 400 mg tablets and placebo. The study team will not be pursuing a change in labeling or an FDA approved indication for this drug as a part of this proposal. Standard placebo provided in similar tablet forms. All investigational drugs will be prepared by the Investigational Pharmacy by inserting the active drug/placebo into larger cloaking capsules. Standard corn starch will be used inside the placebo capsule.

Randomization will be 1:1. The Investigational Pharmacy will be performing randomization and will generate the block randomization scheme.

Endpoints: The primary endpoint is resolution of ARF, defined as a return to baseline creatinine for 24 hours.

The secondary endpoints of progression of ARF to a different stage as defined by AKIN criteria will be assessed.[3] If a patient is enrolled at stage III ARF, they will considered to have progressed should they be started on renal replacement therapy (RRT). Other secondary endpoints that will be assessed include change in serum creatinine from baseline to day 14, combined increase of treatment success and "partial response" which we define as serum creatinine level decreased by >50% from baseline but not to baseline without dialysis or HRS recurrence, transplant free survival at day 30 and 180, overall survival at day 30 and 180, composite survival index at day 30 and 180.

Statistical Methods: All analyses will be conducted based on the intention to treat population. Results will be expressed as means with standard deviations. Chi-squared and Fisher's exact test will be used to analyze our categorical endpoints. Student's t test and Mann-Whitney Rank Sum test will be used for secondary analysis of differences in numerical lab data. Kaplan-Meier curves will be constructed and compared by a log-rank test to assess our secondary endpoints of survival. A p value of <0.05 will be significant. Subgroup analysis will be performed by stratifying on initial AKIN stage.

Future Study: If there is a treatment benefit with using PTX for treatment of ARF in patients with cirrhosis, we would apply for an orphan grant from the NIH or foundation awards from the American Association for the Study of Liver Diseases for a multi or single center, randomized, double blinded placebo controlled trial. Ideally we could combine this with translational research to help better determine a mechanism of action.

1. Introduction and Study Rationale

Chronic liver disease (CLD) is the 12th leading cause of death in the U.S.[8] and is a significant cause of morbidity and hospitalizations across the world. It has been estimated that chronic liver disease represents yearly economic costs in upwards of $2 billion.[9, 10] Acute renal failure (ARF) is one of the most common complications in patients with cirrhosis and leads to poorer outcomes.[11] The onset of ARF is typically in association with other manifestations of hepatic decompensation including gastroesophageal variceal bleeding, spontaneous bacteria peritonitis (SBP), hyponatremia and issues with volume status and can occur in up to 19% of patients hospitalized with cirrhosis.[12] ARF in patients with cirrhosis can be further subtyped into pre-renal azotemia (PRA), acute tubular necrosis (ATN) or Type I or II hepatorenal syndrome (HRS).[13]

HRS is a feared complication of CLD and cirrhosis and presents a unique challenge to physicians and their management. The incidence of HRS in patients with cirrhosis and ascites is 18 and 39 percent at one and five years, respectively.[14] HRS occurs in the absence of underlying kidney disease and leads to renal failure secondary to compensatory renal vasoconstriction due to an ineffective interarteriolar blood volume resultant from splanchnic arterial vasodilation.[15, 16] The prognosis of type 1 HRS is so poor with life expectancy less than 2 weeks.[7] Patients often decompensate and die prior to liver transplant (LT)

The standard of care to treat type I HRS is the combination of albumin, octreotide and midodrine.[17] Terlipressin in combination with albumin is also effective, however, this is not FDA approved or available currently in the U.S.[18] Noradrenalin and albumin may also be used however this requires ICU level care and is not applicable for all patients or all hospitals. [19] Patients who develop HRS and survive are more likely to develop HRS recurrence. After the withdrawal of treatment for type 1 HRS, recurrence can occur in up to 20% of cases.[17] Treatment for PRA or ATN is largely supportive with careful attention to volume status and avoidance of nephrotoxins.

Pentoxifylline (PTX) is a phosphodiesterase inhibitor with anti-inflammatory capabilities that lowers blood viscosity and improves erythrocyte flexibility. Proinflammatory cytokines, including TNF-a and interleukin-6 are elevated in patients with chronic liver disease and cirrhosis in response to circulating endotoxemia.[20, 21] These cytokines lead to a proinflammatory, hyperdynamic state in cirrhosis.

PTX has been shown to decrease levels of TNF-a[22] and has also been shown to increase systemic vascular resistance to oppose the splanchnic vasodilation seen in cirrhosis, but has not had a documented effect on portal pressures.[23]

PTX has is effective in preventing HRS in acute alcoholic hepatitis.[24] In their study of 101 patients, Akriviadis et al demonstrated that compared to placebo, patients randomized to 400mg PTX orally three times a day not only had improved survival

(24.5% versus 46.1% mortality, p = 0.037; RR 0.59, 95% CI 0.35-0.97) but a decreased risk of developing HRS as a cause of death (50% versus 91.7% respectively, p = 0.009; RR 0.29; 95% CI 0.13-0.65). Interestingly, the authors noted that increasing TNF-a levels during the hospital course were associated with an increase in mortality rate.

PTX has been used to treat renal failure from idiopathic membranous glomerularnephropathy[25] and to prevent GFR decline in high-risk chronic kidney disease patients when compared to placebo and thus may have a role in intrinsic kidney disease as well.[26]

Two studies have examined using PTX for HRS prevention in all cirrhotics. In their randomized controlled trial of 335 patients with advanced cirrhosis (Child-Pugh class C), Lebrec et al[27] demonstrated that the proportions of patients without a composite of complications, including HRS, were higher in the PTX group than the placebo group at two (78.6% vs. 63.4%, p = .006) and six months (66.8% vs. 49.7%, p = .002) respectively. Furthermore, the probability of being free of renal failure was statistically significant at 6 months in the PTX group (90.9%, 95% CI 86.1-95.6) versus the placebo group (79.4%, 95% CI 72.6-86.1%), p = 0.02. However, there was no appreciable survival difference at 2 and 6 months between these two groups.

In their landmark study, Tyagi et al[28] demonstrated that PTX is effective in preventing HRS in cirrhotic patients with ascites. In their randomized placebo controlled trial of 70 patients, 35 were given PTX with improvements in serum sodium, mean arterial pressure and preservation of creatinine. Of the 12 patients who developed HRS, two patients were in the PTX arm (type-1 HRS, n = 2) (P = 0.01). The authors noted that patients with HRS had higher baseline TNF-α (15.3±5.8 vs. 10.9±4.8 pg/ml, P = 0.01), lower MAP (68.0±3.8 vs. 77.8±6.5 mmHg, P = 0.01), and sodium level (131.2±3.0 vs. 135.6±4.7 mmol/l, P = 0.003) than those who did not develop HRS.

To our knowledge, no study to date has investigated adding PTX to the treatment algorithm for the treatment of ARF in patients with cirrhosis despite the previously demonstrated benefit of PTX as primary prophylaxis to prevent HRS, a subtype of ARF.[27]

For all of these reasons, we propose a double blind, randomized, placebo controlled pilot trial with PTX to investigate the efficacy of PTX in treating ARF in patients with cirrhosis.

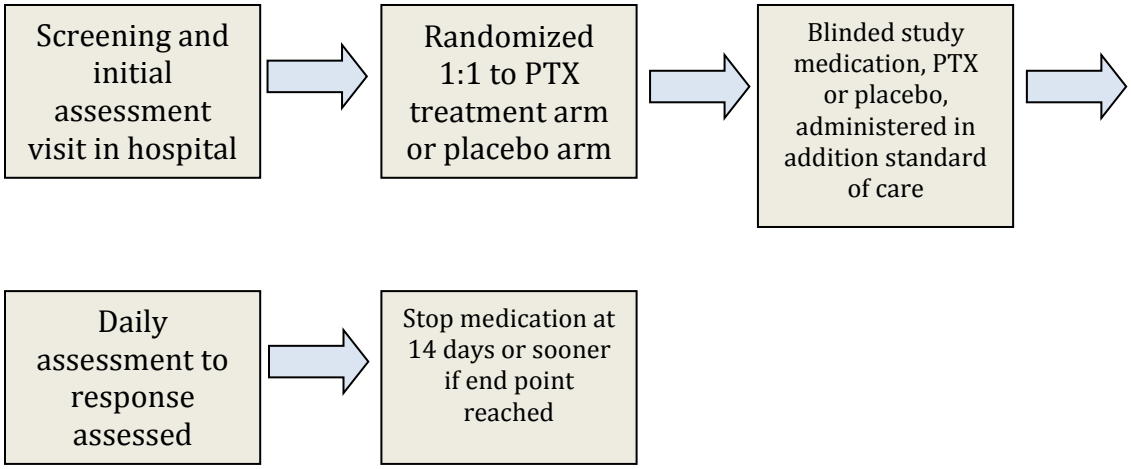
2. Study Design

The proposed study is a blinded prospective, placebo controlled, randomized pilot study. Figure 1 shows the study design schematic. Subjects will be identified during their hospitalization with ARF. Each subject will undergo screening and a pre-dosing history and physical exam, and safety assessment, which will include reviewing basic blood work results and imaging from their hospitalization (CBC, CMP, INR, Blood cultures, UA and urine culture, Urine lytes, Chest x-ray, Abdominal ultrasound with dopplers, diagnostic paracentesis if ascites is present) and performing urine pregnancy testing in women of child bearing potential. Subjects will be randomized 1:1 by the Investigational Pharmacy.

Subjects will then take a 14-day course of PTX 400 mg three times a day. On day 3 there will be an in-person assessment and review of side effect profile. If there have been no serious adverse events, PTX will be continued. Additional safety assessments will be completed at day 7,10,14.

Patients will also be seen in the hospital to assess for treatment response at day 3,7,10,14. At these visits, they will have repeat blood work at the discretion of the treating physicians (e.g. CBC, CMP, INR, UA with reflex urine culture, Urine lytes,).
During each assessment, primary and secondary endpoints will be measured. If an endpoint is obtained, the patient will be instructed to stop therapy.
Survival will be assessed at 30 and 180 days by telephone interviews. If subjects are discharged prior to completing 14 days of therapy, they most likely has met an endpoint (resolution, death, transplant, etc). If in the unlikely event the patient is to be discharged and they have not met an endpoint, they will be withdrawn from the study. Once the patient is discharged there will be no in person follow up evaluations.

Figure 1: Study protocol



3. Subject Selection

This study will enroll 30 patients with cirrhosis hospitalized with acute or chronic liver disease and ARF as defined according to the criteria put forth by and validated prospectively by collaboration between the International Ascites Club (IAC) and the Acute Dialysis Quality Initiative as a rise in creatinine of 0.3 mg/dl or 50% from baseline creatinine, which will be defined as the most recent stable measurement before admission.[1]

All participants will be aged greater than or equal to 18 and non-pregnant because of the study drug characteristics. Patients with labeled contraindications to PTX use will be excluded.

All subjects will be initially located on the general medical floor, typically 5 central which is a GI and hepatology floor. If a subject decompensates and requires ICU level care then they will be transferred to the ICU at the discretion of the treating physician. Admission to the ICU will not impede participation status unless the patient reaches and endpoint of death, liver transplant or renal replacement therapy at which time their participation in the study will have concluded. We will not be performing initially enrollment of the patient in the ICU. We will not seek surrogate consent. If a patient is still in the ICU at day 14 they will not be considered for therapy beyond that point and therefore surrogate consent will not be required.
If a patient is unable to swallow a pill for 6 consecutive doses they will be withdrawn from the study.

Table 1 shows the exclusion criteria.

Table 1: Exclusion criteria

Allergy or hypersensitivity to PTX or intolerance to methylxanthines (e.g. caffeine, theophylline)
Concurrent use of nephrotoxic drugs
Age less than 18
Pregnancy
Acute or chronic renal replacement therapy at time of enrollment
Shock
TNF alpha antagonist use
Subject is institutionalized or a prisoner
Recent cerebral or retinal hemorrhage (contraindication to PTX)
Previous participation in this study
Severe or poorly controlled cardiovascular disease as determined by the principal investigator to hinder the ability to adhere to study protocols
Creatinine > 4.0 g/dL
Life expectancy $\leq$ 72 hours

4. Overall Risk Benefit Assessment

This study is designed to assess the efficacy of PTX use in patients with cirrhosis with ARF when added to standard of hospitalized care. Because of the short duration of dosing and intensive safety assessments, the risks of this study should be minimal to the subjects. Prior studies in both hospitalized and outpatient populations with liver disease have shown PTX to be safe in this population. The risk benefit ratio is minimized in the study design and safety plan.

5. Study Objectives

This study is a randomized placebo controlled trial and is hypothesis based. Data on efficacy will be assessed.

5.1. Primary Objective: PTX is safe and effective in treating ARF in hospitalized patients with cirrhosis when added to standard of care

5.2 Secondary and Exploratory Objectives: Progression of ARF to a different stage as defined by AKIN criteria will be assessed.[3] If a patient is enrolled at stage III ARF, they will considered to have progressed should they be started on renal replacement therapy (RRT). Other secondary endpoints that will be assessed include change in serum creatinine from baseline to day 14, combined increase of treatment success and "partial response" which we define as serum creatinine level decreased by >50% from baseline but not to baseline without dialysis or HRS recurrence, transplant free survival at day 30 and 180, overall survival at day 30 and 180, composite survival index at day 30 and 180.

6. Ethical Considerations

6.1. Good Clinical Practice

This study will be conducted in accordance with Good Clinical Practice (GCP), as defined by the International Conference on Harmonization (ICH) and in accordance with the ethical principles underlying European Union Directive 2001/20/EC and the United States Code of Federal Regulations, Title 21, Part 50 (21CFR50). The study will be conducted in compliance with the protocol. The protocol and any amendments and the subject informed consent will receive Institutional Review Board/Independent Ethics Committee (IRB/IEC) approval/favorable opinion prior to initiation of the study. All potential serious breaches must be reported to the local IRB as required immediately. A serious breach is a breach of the conditions and principles of GCP in connection with the study or the protocol, which is likely to affect, to a significant degree, the safety or physical or mental integrity of the patients of the study or the scientific value of the study. Study personnel involved in conducting this study will be qualified by education, training, and experience to perform their respective task(s).

6.2. Institutional Review Board/Independent Ethics Committee

Before study initiation, the investigator must have written and dated approval/favorable opinion from the IRB/IEC for the protocol, consent form, subject recruitment materials/process (e.g., advertisements), and any other written information to be provided to patients. The investigator or sponsor should provide the IRB/IEC with reports, updates and other information (e.g., expedited safety reports, amendments, and administrative letters) according to regulatory requirements or institution procedures.

6.3. Informed Consent

Investigators must ensure that patients are clearly and fully informed about the purpose, potential risks, and other critical issues regarding clinical studies in which they volunteer to participate. Surrogate consent will be sought if the patient is unable to provide consent due to encephalopathy or lack of capacity. Freely given written informed consent must be obtained from every subject prior to clinical study participation, including informed consent for any screening procedures conducted to establish subject eligibility for the study. The rights, safety, and well being of the study patients are the most important considerations and should prevail over interests of science and society. The consent process will occur in a private room in the hospital. The PI will carefully discuss the risks and benefits of study participation and review study procedures. The PI will make it clear that the subject's standard clinical care will not be affected in any way through participation or non-participation in the study. All questions will be answered prior to signing the informed consent document and the subject will verbalize understanding at the time of consent. The consent process will take approximately 15 minutes.

7. Study Treatments

7.1. Investigational Drug

PTX is a vasoactive xanthine derivative and phosphodiesterase inhibitor that improves peripheral blood flow and enhances peripheral tissue oxygenation. PTX relaxes smooth muscle in peripheral vessels leading to vasodilation. PTX improves red blood cell flexibility, which allows for improved blood flow ability. Importantly, PTX promotes platelet deaggregation and decreases blood viscosity. The summative effects are a decrease in inflammatory mediators. The investigational pharmacy will be used for drug acquisition, storage, and accountability. Subjects will start the protocol with 400mg PTX three times a day for 14 days or the renally dosed equivalent (400mg BID for eGFR 10-50 and 400mg daily for eGFR <10). The investigators will not seek FDA labeling or approved indications for PTX as part of this study; therefore, no IND will be sought for the study drug use in this protocol. There are no restrictions on concurrent drugs other than those listed in the exclusion criteria in Table 1. The study drug cannot be crushed or administered through a nasogastric tube. If a patient is NPO but can swallow safely, they may receive the drug. If they are NPO and have a nasogastric tube in place they will miss the dose.

7.2. Study Drug Discontinuation

Study drug or placebo will be discontinued if a grade 3 adverse event (based on the NCI Common Terminology Criteria for Adverse Events, CTCAE, version 4.0) related to the study drug at the judgment of the PI and medical monitor. The PI will notify the medical monitor of a grade 3 adverse event over the phone and the medical monitor will conduct an independent review with access to the medical record. The medical monitor may interview the patient at the bedside should they deem this necessary. Meetings between the medical monitor and the PI will take place on an as needed basis. One scheduled meeting will take place after 50% enrollment has been completed to review all the reported adverse events.

Study drug or placebo will be discontinued if a grade 4 adverse event or pregnancy occurs during the study protocol or at the request of the subject. If the subject misses a dose and is less than 4 hours late, the subject will be advised to make up the dose. Otherwise, the dose can be omitted and per protocol dosing can resume with the next scheduled administration.

7.3. Management of Study Drug Side Effects

Because of the short duration of study drug administration, side effects are expected to be minimal. Side effects will be assessed and managed directly by the study team. If severe, the study team will discontinue the study drug. Common side effects of PTX include dyspepsia and nausea. More serious, rare side effects include a hypersensitivity reaction and/or arrhythmia.

8. Study Assessments

8.1. Schedule of Visits

The schedule of study assessments and visits is shown in Table 2.

Table 2: Schedule of visits and study protocol assessments

Visit	Screening initial assessment	Follow up assessment	"Partial response" assessment	Phone Call
Day	0	Day 3,7,10,14	Day 14, 28	Day 30,180
Initial history and physical exam	X			
ARF response assessment		X	X	X
Symptom triggered physical exam		X	X	
Interim safety assessment and pill count		X	X	
Labs and imaging	X	X	X	

8.2. Primary Endpoints

ARF treatment response will be assessed according to Table 2. The PI or sub-investigators will perform all assessments and will assess for the presence of side effects or toxicities of the study drug by performing a brief history at each visit and and by performing a targeted physical exam. A phone call to assess 30 and 180-day survival will be completed.

8.3. Secondary Endpoints

The secondary endpoints will be assessed by the PI, or sub-investigators, during telephone assessments and in-person hospital visits as noted in Table 2.

9. Statistical Procedures and Methods

As this is a pilot study and the benefit of PTX in the treatment of ARF has not been studied, we estimate a sample size of 30, 15 in each treatment arm, is sufficient to meet our primary and secondary endpoints. Results will be expressed as means with standard deviations. Chi-squared and Fisher's exact test will be used to analyze our categorical endpoints. Student's t test and Mann-Whitney Rank Sum test will be used for secondary analysis of differences in numerical lab data. Kaplan-Meier curves will be constructed and compared by a log-rank test to assess our secondary endpoint of all-cause mortality. A p value of <0.05 will be significant. Intention to treat analysis will be performed. Subgroup analysis will be performed by stratifying on initial AKIN stage.

10. Adverse Events, Human Safety Measures, and Oversight

10.1. Definitions

An Adverse Event (AE) is defined as any new untoward medical occurrence or worsening of a pre-existing medical condition in a patient or clinical investigation subject administered an investigational (medicinal) product and that does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign, symptom, or disease temporally associated with the use of investigational product, whether or not considered related to the investigational product.

10.2. Serious Adverse Events

A serious AE (SAE) is any untoward medical occurrence that at any dose:

- results in death
- is life-threatening (defined as an event in which the subject was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe)
- requires inpatient hospitalization or causes prolongation of existing hospitalization (see note below for exceptions)
- results in persistent or significant disability/incapacity
- results in a congenital anomaly/birth defect
- is an important medical event (defined as a medical event(s) that may not be Immediately life-threatening or result in death or hospitalization but, based upon appropriate medical and scientific judgment, may jeopardize the subject or may require intervention [e.g., medical, surgical] to prevent one of the other serious outcomes listed in the definition above.) Examples of such events include, but are not limited to, intensive treatment in an emergency room or at home for severe encephalopathy; seizures or convulsions that do not result in hospitalization.)

All pregnancies, regardless of outcome, will be considered a special adverse event (not an SAE). Although overdose and cancer are not always serious by regulatory definition, these events should be reported as an SAE in an expedited manner.

10.3. Assignment of Adverse Event Intensity and Relationship to Investigational Product

All adverse events, including those that are serious, will be graded according to the National Cancer CTCAE version 4.0. The following categories and definitions of causal relationship to study drug as determined by a physician should be used for all BMS clinical study AEs:

- Related: There is a reasonable causal relationship to study drug administration and the AE
- Not related: There is not a reasonable causal relationship to study drug administration and the AE

The expression "reasonable causal relationship" is meant to convey in general that there are facts (e.g., evidence such as de-challenge/re-challenge) or other arguments to suggest a positive causal relationship.

10.4. Collection and Reporting

Adverse events can be spontaneously reported or elicited during open-ended questioning, examination, or evaluation of a subject. (In order to prevent reporting bias, patients should not be questioned regarding the specific occurrence of one or more AEs.) If known, the diagnosis of the underlying illness or disorder should be recorded, rather than its individual symptoms. The following information should be captured for all AEs: onset, duration, intensity, seriousness, relationship to study drug, action taken, and treatment required. If treatment for the AE was administered, it should be recorded on the appropriate CRF page. The investigator shall supply the IRB with any additional requested information, notably for reported deaths of patients. Completion of supplemental CRFs may be requested for AEs and/or laboratory abnormalities that are reported/identified during the course of the study.

10.4.1. Serious Adverse Events

Following the subject's written consent to participate in the study, all SAEs must be collected, including those thought to be associated with protocol-specified procedures. All SAEs must be collected that occur within 14 days of discontinuation of dosing of the study drug. If applicable, SAEs must be collected that relate to any later protocol specified procedure. The investigator will notify the local IRB of any SAE occurring after this time period that is believed to be related to the study drug or protocol-specified procedure. Serious adverse events, whether related or unrelated to study drug, must be reported within local regulatory requirements. An SAE report should be completed for any event where doubt exists regarding its status of seriousness.

10.4.2. Nonserious Adverse Events

The collection of nonserious AE information should begin at initiation of the first dose of study drug. Nonserious AE's will not be required to be reported to the local regulatory board but the PI can report these AE's at his own discretion if an unusual trend or novel finding is revealed. Nonserious AEs should be followed to resolution or stabilization, or reported as SAEs if they become serious. Follow-up is also required for nonserious AEs that cause interruption or discontinuation of study drug, or those that are present at the end of study participation. Patients with nonserious AEs at study completion should receive post-treatment follow-up as appropriate through the PI or through referral to the subject's primary care physician or specialist as appropriate.

10.4.3. Overdose

An overdose is defined as the accidental or intentional ingestion of any dose of a product that is considered both excessive and medically important. All occurrences of overdose must be reported as an SAE (see above):

10.4.4. Pregnancy

Women who are pregnant will be excluded from this pilot study.

10.5. Projected Adverse Events

PTX has been prescribed internationally since 1972 and was first approved by the FDA in 1984. It is generally well tolerated and the incidence of serious adverse events is <1%.[29] Common side effects to commercially available oral PTX include dyspepsia (2.8-9.6%), nausea and vomiting (1.2-28.8%), dizziness (1.9-11.9%), headache (1.2-6.2%).[29] In the only study using PTX in cirrhotics with ascites for HRS prevention, side effects were statistically similar between the PTX arm and the placebo group; dyspepsia occurred in 20% versus 13% (p=0.19), diarrhea and headache occurred in 13% versus 6% (p not significant, number not given).[28] We expect to encounter the previously reported rates of common complications associated with the use of PTX.

10.6. Study Termination, Monitoring, and Data Security

Dr. Brian Behm will serve as the independent medical monitor for the study subjects. The PI reserves the right to terminate any subject from the protocol if he deems the study subject's continued participation will hinder the effective execution of the protocol or places the subject at risk that is not justified. If the SAE's occur in more than 25% of participants, the PI will place on hold further enrollment in the study until review by an independent local regulatory board composed of a Hepatologist, a Gastroenterologist, and another uninvolved physician vote unanimously to continue the study with appropriate binding modifications made and approved by the local IRB. The study database will be maintained on data systems behind secure university firewalls using state-of-the-art data security technology. The PI and sub-investigators will be the only people with access to the

study database and all protected personal data will be stored in a “linked and coded” dataset.

10.7. Subject Benefit and Payment

There are potential medical benefits to the subject in participating in this trial in that the subject may benefit from the treatment of a rare disease with a poor prognosis and limited life expectancy. There is also a general benefit in increasing medical knowledge and potential help of others in future trials. Subjects will not be compensated.

10.8. Inclusion of Women, Children, and Minorities

This study will not enroll children less than 18 years of age because of limited data on PTX use in children. All women and minorities will be eligible for enrollment unless they meet the exclusion criteria in Table 1. The population of chronic liver disease patients is predominantly Caucasian males, however.

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