An Open-Label Pilot Study Evaluating the Safety and Efficacy of Curcumin in Patients with Primary Sclerosing Cholangitis

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Regulatory Sponsor: John Eaton, M.D.
Division of Gastroenterology and Hepatology, Mayo Clinic
200 First Street SW
Rochester, MN 55905
Phone: (507)-284-3917
Eaton.John@mayo.edu

Study Product: CuraMed® BCM-95 curcumin softgel (EuroPharma, Inc.)

Protocol Number: (IRBe) 14-002660

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List of Abbreviations

LIST OF ABBREVIATIONS

AE	Adverse Event
ALK	Alkaline phosphatase
AST	Aspartate aminotransferase (also SGOT)
CCA	Cholangiocarcinoma
CFR	Code of Federal Regulations
CRF	Case Report Form
DSMB	Data and Safety Monitoring Board
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HIPAA	Health Insurance Portability and Accountability Act
IB	Investigator's Brochure
IND	Investigational New Drug Application
IRB	Institutional Review Board
LT	Liver transplantation
PHI	Protected Health Information
PI	Principal Investigator
PSC	Primary sclerosing cholangitis
SAE	Serious Adverse Event/Serious Adverse Experience
SOP	Standard Operating Procedure
UDCA	Ursodeoxycholic acid

Study Summary

Title	An Open-Label Pilot Study Evaluating the Safety and Efficacy of Oral Curcumin in Patients with Primary Sclerosing Cholangitis
Running Title	Curcumin in Patients with Primary Sclerosing Cholangitis
Protocol Number	14-002660
Phase	Phase I/II
Methodology	Open-label
Overall Study Duration	12-18 months
Subject Participation Duration	3 months
Single or Multi-Site	Single Site (Mayo Clinic in Rochester, MN)
Objectives	Determine the safety and efficacy of curcumin and whether it should be considered for further investigation in a randomized study with a larger number of patients.
Number of Subjects	15
Diagnosis and Main Inclusion Criteria	Patients with primary sclerosing cholangitis
Study Product, Dose, Route, Regimen	One 750 mg CuraMed® softgel (EuroPharma, Inc.) by mouth twice a day. Each 750 mg CuraMed® softgel supplies 500 mg of highly bioavailable BCM-95 curcumin.
Duration of Administration	12 weeks
Reference therapy	NA/no pharmacotherapy
Statistical Methodology	Mann-Whitney U test for continuous variables, Chi-square/Fisher's exact test for categorical variables.

1 Introduction

This document is a protocol for a human research study. This study will be carried out in accordance with the applicable United States government regulations and Mayo Clinic research policies and procedures.

1.1 Background

Primary sclerosing cholangitis (PSC) is a chronic, fibro-inflammatory, cholestatic liver disease affecting approximately 25,000 adolescents and adults in the United States and a major indication for liver transplantation (LT).[1-3] PSC leads to end-stage cirrhosis, represents a foremost risk factor for CCA, and carries a median LT-free survival of only 12 years.[4-7] The etiopathogenesis of PSC is unknown, and despite trials of nearly 20 different immunosuppressants and other agents, safe and effective pharmacotherapy has yet to be established.[2] Unlike in other cholestatic liver diseases (e.g. primary biliary cirrhosis), treatment with ursodeoxycholic acid (UDCA) has not been clearly shown to have a beneficial effect in PSC. In addition, high doses of UDCA have been associated with significantly greater adverse outcomes. Although operative treatment with liver transplantation (LT) is effective for PSC, it is available in limited specialty centers and only an option in select patients; even in suitable LT candidates, however, PSC and CCA can recur post-LT.[8-10] Therefore, given the morbidity and mortality of PSC and the challenges associated with operative treatment, safe and effective pharmacotherapy is critically needed. Furthermore, the negative results of previous clinical trials highlight the need to consider targeting alternative pathophysiologic pathways.

Curcumin, the principal curcuminoid of the rhizome turmeric (*Curcuma longa*), is a naturally occurring compound with anti-inflammatory and anti-oxidant properties, among other potentially therapeutic effects.[11-16] In a recent study of the mdr2 knockout murine model of PSC, it was shown that as little as 4 weeks of oral curcumin treatment resulted in a significant decrease in serum liver enzymes as well as histologic disease, including sclerosing cholangitis, ductular proliferation, and fibrosis, all of which are pathologic hallmarks of PSC.[17, 18] Furthermore, curcumin has been shown to decrease cholangiocyte (i.e. biliary epithelial cell) reactivity as well as hepatic myofibroblast activation (i.e. pro-fibrogenic function), both of which are key phenomena in the pathogenesis of PSC.[17, 18] Therefore, there is promising animal model and cultured human cell line evidence that curcumin may represent a safe, effective, and low-cost therapy for patients with PSC.

1.2 Investigational Agent

Curcumin is an orange-red powder that is a mixture of 3 compounds— curcumin, demethoxycurcumin, and bisdemothyxcurcumin.

Forty to eighty-five percent of an oral dose of curcumin passes through the gastrointestinal tract unchanged. The bioavailability of curcumin is greatest in the colon. Hexahydrocurcuminol is the major biotransformed metabolite of curcumin. The major biliary metabolites are tetrahydrocurcumin and hexahydrocurcumin.

Curcumin has been shown in a growing number of *in vitro* and *in vivo* studies to demonstrate biological activity with a variety of potentially medicinal applications, e.g. anti-inflammatory, anti-oxidant, and chemopreventive (i.e. anti-cancer).[11-16] In clinical studies, it is generally administered orally in capsule form, 2-3 times per day.

1.3 Preclinical Data

Emerging insights into the etiopathogenesis of and potential therapeutic approaches for PSC have been facilitated by the growing use of relevant animal models, particularly the mdr2 knockout mouse.[19, 20] Indeed, recent experimental evidence from this model has demonstrated that as little as 4 weeks of treatment with the naturally-occurring compound curcumin results in a significant reduction of serum liver enzymes as well as histologic disease, including sclerosing cholangitis, ductular proliferation, and fibrosis (i.e. pathologic hallmarks of PSC).[17] In addition to the promising mdr2 knockout mouse model data, curcumin has been shown *in vitro* to decrease insult-induced human cholangiocyte reactivity (a characteristic feature in PSC cholangiocytes),[2, 17, 21] attenuate human myofibroblast activation (manifested classically in PSC as peri-ductal "onionskin" fibrosis),[17, 22] and suppress proliferation and induce apoptosis of human CCA cells (which could serve a vital chemopreventive role in PSC patients).[2, 23, 24] Curcumin may also confer therapeutic benefits in PSC patients through other mechanisms, including its antimicrobial activity,[16, 25] as microbiota have been implicated in the pathogenesis of PSC, and indeed 70% of patients with PSC have inflammatory bowel disease, a disorder associated with enteric microbial dysbiosis.[2, 26-28]

1.4 Clinical Data to Date

Curcumin has demonstrated high tolerability, safety, and efficacy in multiple studies including randomized controlled trials involving healthy individuals as well as patients with a variety of hepatic and non-hepatic inflammatory, degenerative, malignant, neuropsychiatric, and other illnesses.[11-15, 29-35] Collectively, these studies have demonstrated anti-inflammatory, hepatoprotective, anti-fibrotic, immunomodulatory, and anti-carcinogenic activities of curcumin. No significant toxicity has been reported following either acute or chronic administration of turmeric extracts at standard doses. In a minority of patients, mild side-effects as nausea, diarrhea, headache, somnolence, and contact dermatitis (with topical use) have been reported.[11-15, 29, 30]

1.5 Dose Rationale and Risk/Benefits

In this pilot study, patients will receive 1500 mg of highly bioavailable BCM-95 curcumin®, which is supplied in one 750 mg CuraMed® softgel (EuroPharma, Inc.), to be taken orally twice a day for 12 weeks. Each softgel contains 500 mg of pure, highly bioavailable curcuminoids. This dose and route is based on recent published clinical trials, wherein curcumin has been found to be well-tolerated, safe, and efficacious in inflammatory and other disorders.[12, 31-33, 35] Although previous studies have studied twice and three times a day regimens, we have chosen to

pursue the former given convenience and ease of adherence for patients and lack of inferiority data with this dosing regimen.

As described above, serious adverse effects have not been reported with even high doses (e.g. 10x higher than those used herein) of curcumin.[14, 29] Mild adverse effects have been reported, however these have been uncommon and resolved with curcumin dose reduction or discontinuation.[11-15, 29, 30, 36] These effects have included: yellow stool, diarrhea, headache, rash, increase in ALK or lactate dehydrogenase.)

2 Study Objectives

Primary Objective: to determine the change in serum Alkaline Phosphatase following 12 weeks of curcumin treatment as a biomarker of therapeutic efficacy.

Secondary Objective: to determine: 1) change in serum AST, total bilirubin, albumin, C-reactive protein, and Mayo PSC risk score following 12 weeks of curcumin treatment compared to baseline values as markers of biochemical improvement; 2) change in self-reported health status, fatigue severity, and pruritus (as assessed by standardized questionnaires) following 12 weeks of treatment compared to baseline values as markers of symptomatic improvement, and 3) the adverse events occurring during 12 weeks of curcumin treatment in patients with PSC.

3 Study Design

3.1 General Design

We propose to conduct an open-label pilot study to preliminarily assess the efficacy and safety of oral curcumin in adult patients with PSC. Fifteen patients with PSC will receive one 750 mg CuraMed® softgel (EuroPharma, Inc.) by mouth twice a day for 12 weeks. Of note, each 750 mg CuraMed® softgel supplies 500 mg of highly bioavailable BCM-95 curcumin. A positive study, based on significant improvement in serum liver biochemistries, will establish the basis for further evaluation of curcumin in a larger, longer-term clinical trial.

Table 1 in section 6 summarizes the patient evaluation and study procedures. Briefly, prior to study entry, a complete history will be obtained and physical examination performed. Serum Alkaline Phosphatase, AST, total bilirubin, albumin, C-reactive protein, complete blood count, and creatinine will be measured. A blood pregnancy test will be performed on female patients of child bearing potential. Standardized questionnaires regarding health status (SF-36 Health Survey and Chronic Liver Disease Questionnaires), fatigue (Fisk Fatigue Impact Scale) and pruritus (5-D Pruritus scale) will be completed by participants at baseline and at 12 weeks. Phone calls will be made to participants weekly during the study, at completion of the study (i.e. at 12 weeks of therapy) and/or early termination, and at two weeks after completion of the study to monitor for any adverse events or effects of the study drug. Study staff will specifically inquire about local and systemic adverse effects including gastrointestinal upset, nausea, diarrhea, signs of anemia (e.g., weakness, fatigue), and rash; during weekly phone or in person

interviews. Participants will be instructed to contact study nurse coordinators with the development of any possible symptoms related to therapy.

3.2 Primary Study Endpoints

The primary study endpoint in this study will be treatment success, as determined by the proportion of PSC patients who experience clinically significant improvement in Alkaline Phosphatase, as defined by: 1) a ≥40% reduction in serum Alkaline Phosphatase (as compared to baseline value)[37] or 2) a decrease in serum Alkaline Phosphatase to less than 1.5 times the upper limit of normal following 12 weeks of curcumin treatment.[38]

Notably, serum Alkaline Phosphatase values have been repeatedly associated with disease response and prognosis,[39-41] thus this readily measured biochemical test is an important endpoint and biomarker in studies of patients with PSC.

3.3 Secondary Study Endpoints

Secondary efficacy endpoints will include change in: 1) serum AST, total bilirubin, albumin, C-reactive protein, and Mayo PSC risk score[42] following 12 weeks of curcumin treatment compared to baseline values as markers of biochemical improvement and 2) change in self-reported health status, fatigue severity, and pruritus (as assessed by standardized questionnaires) following 12 weeks of treatment compared to baseline values as markers of symptomatic improvement.

3.4 Primary Safety Endpoints

We will monitor for adverse events occurring during 12 weeks of curcumin treatment as part of this study. In addition, occurrence of any of the following will be considered a treatment failure:

- Deterioration of liver biochemistries (doubling of bilirubin and/or increase in AST, ALT, and alkaline phosphatase levels ≥ 3x upper limit of normal or baseline levels without mechanical obstruction)
- Voluntary drug/study discontinuation for any reason (e.g. worsening of fatigue or pruritus or development of diarrhea, headache, nausea, or rash)
- Death
- Liver transplantation

4 Subject Selection Enrollment and Withdrawal

4.1 Inclusion Criteria

Inclusion criteria will be as follows:

- Diagnosis of PSC established by all of the following criteria:[27, 43]
    - ALK >1.5x upper limit of normal for at least 6 months prior to study enrollment

    - Cholangiography demonstrating intrahepatic and/or extrahepatic biliary dilation, beading, and/or strictures consistent with PSC
- Age 18-75 years
- Male or female sex
- Women of child-bearing potential willing to use birth control for the duration of the study
- Informed consent provided by the patient for study participation

4.2 Exclusion Criteria

Exclusion criteria will be as follows:[27]

- Treatment with any investigational agents within three months prior to or during the study.
- Known or suspected cholangiocarcinoma
- Untreated dominant stricture within past 3 months
- Suspected bacterial cholangitis within past 3 months
- Known decompensated cirrhosis.
- Uncontrolled inflammatory bowel disease defined by ongoing symptoms requiring escalation of medical therapy within past 3 months
- Treatment with systemic corticosteroids, colchicine, methotrexate, cyclosporine, chlorambucil, pentoxifylline, or tacrolimus, within three months prior to or during the study.
- Changes in Azulfidine, azathioprine, budesonide, or vitamin E therapies within three months prior to study enrollment.
- Treatment with systemic antibiotics within one month prior or during study.
- Concomitant treatment with NSAIDS, and anticoagulant warfarin.
- Changes in antiplatelet agents or antihyperlipidemics therapies within three months prior to study enrollment.
- Anticipated need for liver transplant within one year as determined by Mayo PSC risk score (<80% one-year survival without transplant)
- Active drug or alcohol use
- Findings suggestive of liver disease of an alternative or concomitant etiology, such as autoimmune hepatitis, chronic alcoholic liver disease, chronic hepatitis B or C infection, hemochromatosis, Wilson's disease, α1-antitrypsin deficiency, non-alcoholic steatohepatitis, primary biliary cirrhosis, or secondary sclerosing cholangitis (e.g. post-LT biliary stricture)
- Pregnancy or lactation
- Extremes of age (younger than 18 or older than 75 years of age).
- Any condition that, in the opinion of the investigator, would interfere with the patient's ability to complete the study safely or successfully

4.3 Subject Recruitment, Enrollment and Screening

Patients with a diagnosis of PSC will be recruited by the study staff in the Division of Gastroenterology and Hepatology at Mayo Clinic) and enrolled in the study if satisfying the above inclusion and exclusion criteria. A total of 15 patients will be enrolled.

4.4 Early Withdrawal of Subjects

Study participants may decide to withdraw from the study at any time; in such case, they will be asked to notify the study team so that they may be advised as to whether any additional tests may be needed to be performed for their safety. Study investigators may withdraw participants from the study at any time if it is considered in a patient's best interest or if a patient does not follow the study protocol. Additional details are provided below.

4.4.1 When and How to Withdraw Subjects

Participants will be withdrawn from the study if they experience a CTCAE 4.0 criteria grade 3 or higher adverse event, are unable to adhere to the study protocol, inadvertently become pregnant during the study (in which case they will be referred to their primary physician for obstetric care), or experience treatment failure as described in section 3.4 above.

Participants may voluntary withdraw from the study for any reason. Patients who withdraw from the study (or decline participation) will not be penalized in any way. Specifically, they do not have to be in this study to receive or continue to receive medical care from Mayo Clinic.

4.4.2 Data Collection and Follow-up for Withdrawn Subjects

Patients who withdraw from (or complete) the study will be followed for a minimum of 2 weeks (to ensure safety) as part of the study in addition to longitudinal routine clinical care.

5 Study Drug

5.1 Description

The study drug will be administered in the form of a capsule (softgel).

5.2 Treatment Regimen

Participants will receive one 750 mg CuraMed® BCM-95 curcumin softgel (EuroPharma, Inc.) by mouth twice a day for 12 weeks.

5.3 Method for Assigning Subjects to Treatment Groups

This will be an open-label pilot study with one treatment group.

5.4 Preparation and Administration of Study Drug

The study drug will be prepared by EuroPharma, Inc. The drug will be stored in the Mayo Clinic Pharmacy and dispensed in the Mayo Clinic Hepatology Clinic, Division of Gastroenterology of Hepatology, by the study coordinator (and/or co-investigators).

5.5 Subject Compliance Monitoring

Adherence will be tracked by the study coordinator using telephone calls weekly. The patient will be asked specifically about compliance with the study drug schedule. If the patient is not deemed by the study investigators to be compliant based on phone call assessment, the patient will be withdrawn from the study but still followed (intention to treat). A decision regarding non-compliance will be determined by the following: the patient has acknowledged being off the study drug for more than two weeks without reason or has been unable to be contacted by the study coordinator or study physician for greater than 6 consecutive weeks.

5.6 Prior and Concomitant Therapy

Potential participants will be excluded if they receive or have received:

- Treatment with any investigational agents within three months prior to or during the study.
- Treatment with UDCA, systemic corticosteroids, colchicine, methotrexate, cyclosporine, chlorambucil, pentoxifylline, or tacrolimus within three months prior to or during the study.

5.7 Packaging

The study drug will be packaged with a label stating “Caution: New Drug--Limited by Federal (or United States) law to investigational use only", instructions for use, i.e. “Take one 750 mg CuraMed® curcumin softgel by mouth twice a day”, and the Mayo Clinic protocol number. The amount of softgels will also be written on the label (12 week supply, i.e. 168 softgels).

5.8 Blinding of Study

NA—open-label study.

5.9 Receiving, Storage, Dispensing and Return

5.9.1 Receipt of Drug Supplies

The study drug will be shipped via UPS by EuroPharma, Inc., under the oversight of [redacted], Chief of Scientific Affairs and Education, Green Bay, WI), to the Mayo research pharmacy at Mayo Clinic.

Upon receipt of the study drug, an inventory will be performed and a drug receipt log filled out accepting the shipment. Any discrepancies from the shipping invoice or damaged or unusable study drug in a given shipment will be documented in the study files. The sponsor and investigators will be notified immediately of any discrepancies, damaged or unusable products that are received.

5.9.2 Storage

The study drug will be stored in a 4°C refrigerator in the dark in the institutional research pharmacy until it is dispensed. This is a secure location with limited access to prevent unintended or unauthorized use. No special handling precautions are otherwise necessary.

5.9.3 Dispensing of Study Drug

A 12 week supply of the study drug will be assigned and dispensed to each study participant. Drug reconciliation checks will be performed by the study team and documented in the medical record. Subjects will be requested to mail in any unused study drug if unable to return for the 12 week visit.
Return or Destruction of Study Drug

At the completion of the study, there will be a final reconciliation of drug shipped, drug dispensed, drug returns, and drug remaining. This reconciliation will be documented in the study file. Study drug destroyed on site per Mayo Pharmacy policy.

6 Study Procedures

Study procedures are summarized in section 3.1 as well as in Table 1.

Screening Visit (-28 to Day 0)

Screening assessments will be completed within 28 days of the baseline/Day 1 visit.
The following procedures will be performed and documented:

- Obtain signed informed consent
- Determine inclusion eligibility
- Obtain medical history
- Perform complete physical examination
- Obtain body height and weight
- Obtain vital signs (resting blood pressure, pulse, respiratory rate and temperature)
- Obtain details of concomitant medications
- Obtain blood samples for
  - Alkaline phosphatase
  - AST

ALT
Total bilirubin
C-reactive protein
Complete blood count (CBC)
INR
Sodium
Creatinine
Albumin
Stored serum
Serum pregnancy test for females of childbearing potential only

Questionnaires
Health status
Pruritus
Fatigue

Subjects meeting all of the inclusion criteria and none of the exclusion criteria will return to the clinic for the Baseline/Day 1 visit.

Treatment Assessments

Baseline/Day 1 Visit
Dispense study medication
Instruct the subject on the packaging, storage and administration of the study drug
If indicated, observe the subject take the first dose of the study drug

Week 3 (+- 7 days)

Obtain blood samples for
Alkaline phosphatase
AST
Total bilirubin
C-reactive protein
Complete blood count (CBC)
Creatinine
Albumin

Phone call or visit to assess for AEs, concomitant medications, and study drug compliance. Note a local laboratory can be used for obtaining the blood samples if subject is unable to return to Mayo.

Week 8 (+- 7 days)
Phone call to assess for AEs, concomitant medications, and study drug compliance. Note a local laboratory can be used for obtaining the blood samples if subject is unable to return to Mayo.

Week 12 (+- 7 days) or Early Termination

Obtain blood samples for
- Alkaline phosphatase
- AST
- ALT
- Total bilirubin
- C-reactive protein
- Complete blood count (CBC)
- INR
- Creatinine
- Sodium
- Albumin
- Stored serum

Questionnaires
- Health status
- Pruritus
- Fatigue

Phone call to assess for AEs, concomitant medications, and study drug compliance. Note a local laboratory can be used for obtaining the blood samples if subject is unable to return to Mayo. Questionnaires can be mailed to subject if unable to return to Mayo or respond over the phone. Remaining study medication can be returned by mail to study team.

Post Treatment Assessment Week 14 (+- 7 days) (2 weeks after stopping study medication)

Phone call to assess for AEs, concomitant medications

Table 1. Patient evaluation and study procedures

n=20 patients with PSC	**Entry**	**3 weeks**	**8 weeks**	**12 weeks**	**2 weeks after study completion (i.e. 14 weeks)**
Medical history and physical examination	X				
Serum laboratory tests*					
ALK	X	X		X	
AST	X	X		X	
ALT	X			X	
Total bilirubin	X	X		X	
C-reactive protein	X	X		X	
Complete blood count	X	X		X	
INR	X			X	
Creatinine	X	X		X	
Sodium	X			X	
Albumin	X	X		X	
Stored serum **	X			X	
Pregnancy test ***	X				
Questionnaires					

Health status	X			X	
Pruritus	X			X	
Fatigue	X			X	
Phone calls†		X	X	X	X

* At study entry, approximately 2 teaspoons of blood will be collected for biochemical testing. At 3 and 12 weeks, approximately 1 teaspoon will be collected for biochemical testing.
**Serum collected at baseline and at the conclusion of the study will be stored for potential future assays to explore mechanisms of action in the pathogenesis of PSC if the study drug seems beneficial.
***For female patients only.
†Will be performed for safety and compliance monitoring as described above and documented accordingly.

7 Statistical Plan

7.1 Sample Size Determination

Approximately 5% of patients with PSC and chronically (>6 months) elevated ALK will spontaneously experience either a clinically significant reduction in serum ALK to less ≤1.5 times the upper limit of normal[38] or a reduction of > 40% of the baseline ALK value.[37] In this open-label pilot study, our primary objective is to determine the proportion of patients who experience curcumin treatment success, as defined by either of these two ALK endpoints. Notably; these patients are hereinafter considered historical controls.[39] Therefore, if treatment success is achieved in at least 30% of curcumin treated patients, i.e. a rate that is at least 25% more than the conservative estimate in historical controls, likely based on pre-clinical data, and clinically promising, this would encourage further study of curcumin in larger, randomized clinical trials in patients with PSC.

By enrolling 15 patients with PSC in our study, an exact binomial test with a nominal two-sided significance level of α=0.05 will have approximately 90% power to detect a 25% difference in clinically significant ALK improvement between the null hypothesis of 5% (historical control) and the alternative hypothesis of 30%. In addition, if 6 of 20 PSC patients (30%) experience treatment success, the 95% exact binomial confidence interval (CI) would be 11.9% to 54.3%, suggesting that the sample size has adequate precision to not include the null hypothesis (5%) in the CI.

7.2 Statistical Methods

Univariate descriptive statistics and frequency distributions will be calculated, as appropriate, for all variables. Baseline values for demographic, clinical, and outcome variables (primary and secondary) will be tabulated. These analyses will help identify potential confounding variables to be used as covariates in advanced statistical (e.g. multivariate) analyses. Bonferroni correction will be used to adjust p-values in the case of multiple comparisons.

7.3 Subject Population(s) for Analysis

The study participants whose data will be subjected to data analysis include:

- All-treated population: Any subject entered into the study that received at least one dose of study drug.
- All-completed population: Only subjects who completed all study related procedures and follow-up will be included

8 Safety and Adverse Events

8.1 Adverse events and study discontinuation

Patients will be discontinued from the study if they: 1) request withdrawal from the study, 2) develop worsening of underlying liver function defined as doubling of serum total bilirubin and/or increase in ALK or AST to ≥ 3x the upper limit of normal or baseline levels without mechanical biliary obstruction, 3) have side effects to study drug (e.g. diarrhea) that are not controlled by over the counter medication (e.g. loperamide), or 4) experience an adverse event based on CTCAE 4.0 criteria of grade 3 or higher that is not related to underlying disease.

When an adverse event has been identified, the study team will take appropriated action necessary to protect the study participant and then complete the Study Adverse Event Worksheet and log. The investigators will evaluate the event and determine the necessary follow-up and reporting required (see next section).

8.1.1 Investigator reporting

The investigators will personally supervise the study. An adverse event is defined as any unfavorable and unintended diagnosis, symptom, or disease temporarily associated with use of the study medication, whether or not related to the medication. Worsening of the pre-existing clinical condition will be considered an adverse event and, possibly, treatment failure.

The investigators will use the following definitions to assess the relationship of the adverse event to the use of study drug:

1. Probably related: Adverse event has a strong temporal relationship to study drug or recurs on re-challenge and another etiology is unlikely or significantly less likely.
2. Possibly related: Adverse event has a strong temporal relationship to the study drug and an alternative etiology is equally or less likely compared to the potential relationship to study drug.
3. Probably not related: Adverse event has little or no temporal relationship to the study drug and/or a more likely alternative etiology exists.
4. Not related: Adverse event is due to an underlying or concurrent illness or effect of another drug and is not related to the study drug (e.g., has no temporal relationship to study drug or has a much more likely alternative etiology).

Adverse events will be classified according to severity into: mild (transient and easily tolerated by the participant), moderate (causes the participant discomfort and interrupts the

participant's usual activities), or severe (causes considerable interference with the participant's usual activities and may be incapacitating or life-threatening). A serious adverse event is defined as any untoward medical occurrence that results in death, is life-threatening, requires or prolongs hospitalization, causes persistent or significant disability/incapacity, or, in the opinion of the investigators, represents other significant hazards or potentially serious harm to research participants.

The investigators will be responsible for communicating adverse events to the Mayo Institutional Review Board (IRB), the Data and Safety Monitoring Board, Co-investigators, and the Food and Drug Administration. The following information will be recorded in the study database and provided as indicated:

- Medical record number:
- Disease/histology (if applicable):
- The date the adverse event occurred:
- Description of the adverse event:
- Relationship of the adverse event to the research (drug, procedure, or intervention):
- If the adverse event was expected:
- The severity of the adverse event: (use a table to define severity scale 1-5)
- If any intervention was necessary:
- Resolution: (was the incident resolved spontaneously, or after discontinuing treatment)
- Date of Resolution:

8.1.2 Investigator reporting: Notifying the FDA

The investigators will report to the FDA all unexpected, serious suspected adverse reactions according to the required IND Safety Reporting timelines, formats and requirements.

Unexpected fatal or life threatening suspected adverse reactions where there is evidence to suggest a causal relationship between the study drug/placebo and the adverse event, will be reported as a serious suspected adverse reaction. This will be reported to the FDA on FDA Form 3500A, no later than 7 calendar days after the investigator's initial receipt of the information about the event.

Other unexpected serious suspected adverse reactions where there is evidence to suggest a causal relationship between the study drug/placebo and the adverse event, will be reported as a serious suspected adverse reaction. This will be reported to the FDA on FDA Form 3500A, no later than 15 calendar days after the investigator's initial receipt of the information about the event.

Any clinically important increase in the rate of serious suspected adverse reactions over those listed in the protocol or product insert will be reported as a serious suspected adverse reaction. This will be reported to the FDA on FDA Form 3500A no later than 15 calendar days after the investigator's initial receipt of the information about the event.

Findings from other studies in human or animals that suggest a significant risk in humans exposed to the drug will be reported. This will be reported to the FDA on FDA Form 3500A, no later than 15 calendar days after the investigators initial receipt of the information about the event.

8.2 Stopping Rules

The study will be stopped if two or more participants develop an adverse event based on Common Terminology Criteria for Adverse Events (CTCAE) 4.0 criteria of grade 3 or higher OR if one patient develops an adverse event based on CTCAE 4.0 criteria of grade 4 or higher that is not related to the participant's underlying disease.

8.3 Medical Monitoring

It is the responsibility of the principle investigators to oversee the safety of the study at their site. This safety monitoring will include careful assessment and appropriate reporting of adverse events as noted above, as well as the construction and implementation of a site data and safety-monitoring plan (see section 10 "Study Monitoring, Auditing, and Inspecting"). Medical monitoring will include a regular assessment of the number and type of serious adverse events.

9 Data Handling and Record Keeping

9.1 Confidentiality

Information about study subjects will be kept confidential and managed according to the requirements of the Health Insurance Portability and Accountability Act of 1996 (HIPAA). Confidentiality of patient information will be protected by using a study number to identify participants. Data collection forms will be kept in locked files designated for this study within an office, and computerized data will be password-secured.

9.2 Records Retention

The investigators will maintain records and essential documents related to the conduct of the study. These will include subject case histories and regulatory documents.

The investigators will retain the specified records and reports for;

1. Up to 2 years after the marketing application is approved for the drug; or, if a marketing application is not submitted or approved for the drug, until 2 years after shipment and delivery of the drug for investigational use is discontinued and the FDA has been so notified or
2. As outlined in the Mayo Clinic Research Policy Manual –"Access to and Retention of Research Data Policy" http://mayocontent.mayo.edu/research-policy/MSS_669717 , whichever is longer

10 Study Monitoring, Auditing, and Inspecting

10.1 Study Monitoring Plan

The investigator will allocate adequate time for such monitoring activities. The Investigator will also ensure that the monitor or other compliance or quality assurance reviewer is given access to all the study-related documents and study related facilities (e.g. pharmacy, diagnostic laboratory, etc.), and has adequate space to conduct the monitoring visit.

This study will be monitored on a routine basis during the conduct of the trial. The Mayo Clinic Office of Research Regulatory Support will be allowed to provide clinical monitoring for the trial as a service for the sponsor-investigator. Clinical trial monitoring requires review of the study data generated throughout the duration of the study to ensure the validity and integrity of the data along with the protection of human research subjects. This will assist sponsor-investigators in complying with Food and Drug Administration regulations.

10.2 Auditing and Inspecting

The investigator will permit study-related monitoring, audits, and inspections by the IRB, the sponsor, and government regulatory agencies, of all study related documents (e.g. source documents, regulatory documents, data collection instruments, study data etc.). The investigator will ensure the capability for inspections of applicable study-related facilities (e.g. pharmacy, diagnostic laboratory, etc.).

Participation as an investigator in this study implies acceptance of potential inspection by government regulatory authorities and applicable compliance offices.

11 Ethical Considerations

This study is to be conducted according to United States government regulations and Institutional research policies and procedures.

This protocol and any amendments will be submitted to a properly constituted local Institutional Review Board (IRB), in agreement with local legal prescriptions, for formal approval of the study. The decision of the IRB concerning the conduct of the study will be made in writing to the sponsor-investigator before commencement of this study.

All subjects for this study will be provided a consent form describing this study and providing sufficient information for subjects to make an informed decision about their participation in this study. This consent form will be submitted with the protocol for review and approval by the IRB for the study. The formal consent of a subject, using the Approved IRB consent form, must be obtained before that subject undergoes any study procedure. The consent form must be signed by the subject or the subject's legally authorized representative, and the individual obtaining the informed consent.

12 Study Finances

12.1 Funding Source

This study will be funded by Europharma.

12.2 Conflict of Interest

None.

Any study team member who has a conflict of interest with this study (patent ownership, royalties, or financial gain greater than the minimum allowable by their institution, etc.) arise will have the conflict reviewed by a properly constituted Conflict of Interest Committee with a Committee-sanctioned conflict management plan that has been reviewed and approved by the study sponsor-investigator prior to participation in this study.

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