A Phase II Trial of Pentoxifylline in Newly-Diagnosed Biliary Atresia

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Last approved by the Baylor College of Medicine Institutional Review Board: June 7, 2022
Clinical Trials # NCT01774487

Precis

Biliary atresia (BA) is a devastating liver disease of infancy of unknown etiology, characterized by bile duct obstruction, live fibrosis, and cirrhosis. BA has no known medical treatments. The only proven treatment is a surgical portoenterostomy (the Kasai procedure, or KP) which can achieve bile drainage and improve outcomes in some cases. The KPs success is variable depending on several factors including age of the infant, experience of the surgeon, and extent of liver fibrosis at the time of KP.

In this study, we conduct a phase II trial of a potential new medical therapy for BA: pentoxifylline (PTX). PTX is a methylxanthine derivative closely related to caffeine that has been used safely in infants with other diseases such as sepsis. In adults, PTX has been shown to have a number of properties beneficial to the liver, including preventing liver fibrosis, improving liver regeneration, and reducing cirrhosis-related complications.

The trial's objective is to determine whether PTX has sufficient biological activity against BA to warrant further study. PTX will be administered orally for 90 days as an adjunct to standard therapy (i.e. KP if appropriate). The primary outcome will measure the change in serum conjugated bilirubin levels after 90 days. Secondary outcomes include changes in body weight, serum markers, liver imaging, and time to liver transplant in infants with BA.

Table of Contents

A. Objectives 4

B. Background and Rationale 4

C. Enrollment Procedures

i. Inclusion Criteria 4

ii. Exclusion Criteria 5

iii. Pre-treatment Evaluation 5

iv. Patient Registration 5

D. Study Implementation

i. Study Design 5

ii. Drug Administration 6

iii. Required Observations 6

iv. Dose Modifications 6

v. Concurrent Treatments 6

vi. Removal of Patients from Study 6

E. Data Collection

i. Clinical Data 6

ii. Adverse Events 6

F. Statistical Considerations

i. Overview 6

ii. Sample-Size Calculations 7

G. Ethical Issues 8

H. Pharmaceutical Information 8

I. References 10

J. Appendix

i. Data Safety Monitoring Plan 12

ii. Consent 14

A. Objectives

1) To determine whether a 90 day course of oral PTX can improve serum conjugated bilirubin levels in infants with newly-diagnosed BA and receiving standard care

2) To describe how PTX therapy affects body weight, serum markers, liver imaging, and time to liver transplantation in infants with BA

B. Background and Rationale

In the US and around the world, biliary atresia (BA) is the most common reason why children require a liver transplant (LT).[1, 2] BA develops early for unknown reasons, appearing in one in 10,000 infants during the first weeks of life. The disease's hallmark feature is bile duct obstruction, which causes bile to back-up and damage the liver. Within months, it progresses to liver fibrosis, cirrhosis, and eventually end-stage liver disease. Hence, without LT, BA becomes incompatible with life.

New therapies that delay or prevent LT are lacking. BA's only therapy – the Kasai portoenterostomy (KP) – was devised in the 1950's in an attempt to restore bile flow.[3] The surgery involves removing the obstructed bile ducts and connecting the liver directly to the small intestine. The KP has been shown to improve outcomes in BA. However, its success is variable, depending on a number of factors including age of the child, experience of the surgeon, and extent of pre-existing liver damage.[4, 5] When the KP is unsuccessful, the only remaining treatment is LT.

In this study, we evaluate a novel medical therapy for BA: the methylxanthine derivative pentoxifylline (PTX). PTX has a number of properties that could prevent further liver damage in BA patients. In cell culture PTX inhibits the fibrotic response, and in animal BA models PTX reduces liver fibrosis while promoting weight gain.[6, 7] In humans, PTX improves indices in fatty liver disease, promotes regeneration after liver resection, and reduces morbidity in cirrhotic patients.[8-10] Importantly, in multiple studies with septic neonates, PTX caused no serious adverse events.[11]

We hypothesize that PTX will reduce liver damage in patients with BA. To test this, we will compare serum conjugated bilirubin levels (CB) before and after 12 weeks of PTX therapy. Bilirubin levels are an accepted surrogate for cholestasis and liver damage in BA.[2, 4, 12] Elevated CB levels reflect two pathological processes: (i) persistent bile back-up from duct blockage, and (ii) impaired bilirubin conjugation from hepatocyte damage. Improving CB levels suggest improving liver function and a better prognosis.[2, 4, 5] In our group, 90.4% patients with normal CB levels three months post-KP survived at least two years without needing a LT (n = 21, patients seen between 2006-2010, unpublished data).

We will test PTX using the two-stage "minimax" Phase 2 clinical trial design originally described by Simon.[13] Phase 2 studies have been most commonly used to determine whether chemotherapeutic agents have sufficient activity to warrant a larger Phase 3 clinical trial. The two-stage "minimax" design identifies therapies with large effects, and has two distinct advantages compared to other designs: (i) early termination if the drug is not efficacious, and (ii) smaller sample sizes without the need for a control arm.

C. Enrollment Procedures

i. Inclusion Criteria (all must be met)

	Criteria	Requirement
□	Age	0-180 days old
□	Diagnosis	Liver biopsy (if inconclusive, intra-operative cholangiogram)

□	Prior Therapy	No previous KP performed at another institution
□	Overall Health	Able to take medications orally
□	Informed Consent	Legal guardian signs consent (see Consent in appendix) after understanding risks and investigational nature of study

ii. Exclusion Criteria

a) Infants greater than 180 days old
b) Infants receiving a KP at another institution
c) Infants unable to take medications orally

iii. Pre-treatment Evaluation

Serum

□ Liver panel (including conjugated bilirubin and GGT)
□ Complete blood count with differential
□ Coagulation profile (PT, PTT, INR)
□ Chemistry Panel (including electrolytes and creatinine)
□ Pre-albumin
□ 25-hydroxy Vitamin D

Imaging

□ Complete abdominal ultrasound with Doppler and spleen/liver size measurements

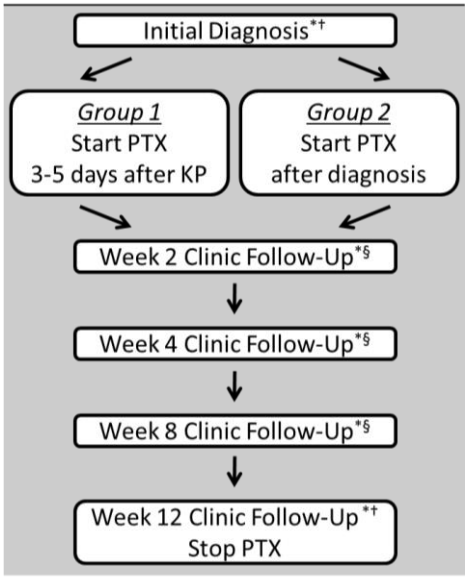
Procedures

□ KP if deemed eligible by hepatologists and surgeons (Group 1 patients)

iv. Patient Registration – Contact Dr. Sanjiv Harpavat (832-824-2099 pager 2144)

D. Study Implementation

i. Study Design



* Measure weight, liver panel, complete blood count, coagulation profile, chemistry, pre-albumin levels
† Measure vitamin D levels, liver size, spleen size
§ Increase PTX according to weight

ii. Drug Administration

a) Dosage: 20 mg/kg/day divided q 8 hours (i.e., 6.6 mg/kg/dose q 8 hours), in accord with a previous studies in children for other indications[14]

b) Formulation: 20 mg/ml solution made by crushing commercially available PTX 400 mg tablets (Teva Pharmaceuticals USA, Sellersville, PA) and diluting per established recipe written by Nahata MC, Pediatric Drug Formulation, 5th Edition, pg. 215.

iii. Required Observations

	Week 2	Week 4	Week 8	Week 12
Weight	□	□	□	□
Liver panel	□	□	□	□
Complete Blood Count	□	□	□	□
Coagulation Profile	□	□	□	□
Chemistry Panel	□	□	□	□
Pre-Albumin	□	□	□	□
25-OH Vitamin D				□
Liver Ultrasound				□
Adjust PTX dose	□	□	□	

iv. Dose Modifications – Increase according to weight at clinic visits 2, 4, and 8 weeks after starting PTX

v. Concurrent Treatments

a) Standard therapies: All standard therapies will be given during PTX therapy, including ursodiol, fat-soluble vitamins, and post-KP antibiotics

b) Experimental therapies: No other experimental therapies will be given during PTX therapy

vi. Removal of Patients from Study

a) Non-medical reasons: Parents may voluntarily exclude their infant from the study at any time; in addition, patients may be removed from the study if they are not compliant with taking PTX as prescribed

b) Medical reasons: In the event of a serious adverse event, the study team and the IRB will determine whether the patient should be removed from the study (see Data Safety Monitoring Plan in appendix)

E. Data Collection

i) Clinical Data – All clinical data (weights, laboratory results, imaging results) will be stored in the patient's electronic medical record

ii) Adverse Events – All adverse events reported by parents or noted by physicians will be recorded in the patient's medical record. They will also be reported to the IRB following a pre-determined schedule (see Data Safety Monitoring Plan in appendix)

F. Statistical Considerations

i) Overview

This is a Phase 2 clinical trial using the two-stage "minimax" design described by Simon.[13] As a Phase 2 trial, the trial's objective is to determine whether PTX has sufficient biological activity against BA to warrant further study. By choosing the two-stage "minimax" design, we gain two advantages: (i) early termination if the drug is not efficacious, and (ii) an overall smaller sample size to test the hypothesis. One limitation is that the design identifies only large effects (response >20%). For BA this is appropriate, because the field is in need of a robust therapy that can substantially limit liver damage and delay/prevent need for LT.

The Phase 2 design involves administering PTX to all subjects and comparing their response to historical controls. Hence, the study has no randomization or control arm. Historical controls from BA patients seen at Texas Children's hospital between 2006-2010 will be used. Of those receiving the KP (equivalent to Group 1 study subjects), 21/36 or 58.3% had normal CB levels 3 months post-KP. This agrees with previously published figures from other centers.[15] Of those not receiving the KP (equivalent to Group 2 study subjects), 1/13 or 7.7% had stable CB levels after 3 months.

Historical controls in this study are appropriate for a number of reasons. The same two pediatric surgeons performing all of the KPs in the past will perform the KPs for future study subjects. Furthermore, neither the KP surgical technique nor our medical management of patients with BA has changed over the years. Rather, the only difference is that the number of patients with BA seen at Texas Children's Hospital has increased. One potential bias that may arise is that we may be more vigilant to ensure study subjects take PTX, which may lead to more overall care. To control for this, we will adhere to the same clinic schedule and guidelines as we have used in the past.

In this study, Group 1 and Group 2 patients will be analyzed independently:

Group 1) Infants receiving the KP will be given PTX for 12 weeks, and the number whose CB levels return to normal (0.0-0.3 mg/dL) will be calculated. Historically, as mentioned above, ~60% of such infants have normal CB levels after 12 weeks. The study will determine whether PTX improves this percentage.

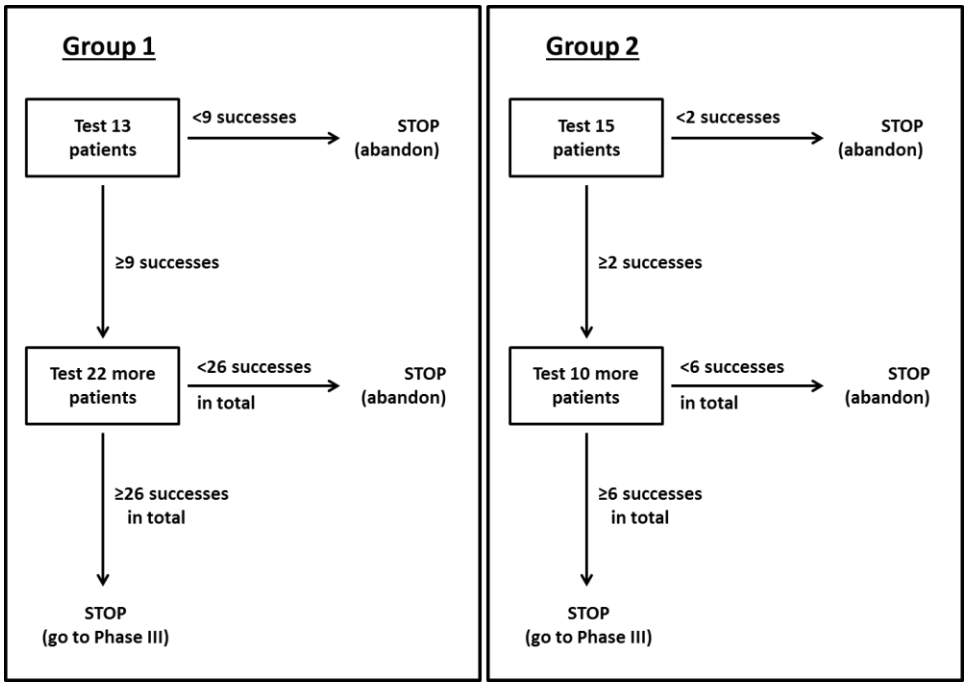
Group 2) Infants not receiving the KP will be given PTX for 12 weeks, and the number whose CB levels stabilize (within 10% of starting level) will be calculated. Historically, as mentioned above, ~10% of such infants have stable CB levels after 12 weeks. The study will determine whether PTX improves this percentage.

ii) Sample-Size Calculations

For sample size calculations, we use previously-derived tables for the "minimax" design for two-stage studies described by Simon.[13] Because BA is in need of a robust therapy, we designed the study to detect a large effect (>20% increase in responders). We used standard values for significance (alpha = 0.05) and power (beta = 0.2). Our total sample size is the sum of patients needed in Groups 1 and 2 (35 and 25, respectively).

For Group 1, approximately 60% of patients receiving the KP have a normal CB (0.0-0.3 mg/dL) 12 weeks later based on historical data (null hypothesis). We are interested in determining whether PTX can increase this to 80% of patients (alternative hypothesis), which would be a large enough response to make the medication worth pursuing in a larger Phase 3 trial. To test the null hypothesis versus the alternative hypothesis at a significance level of 0.05 and power of 80%, 35 patients must be enrolled. Of these 35, 26 or more patients must respond to reject the null hypothesis. Furthermore, the study will be terminated early if, of the first 13 patients, fewer than 9 respond.

For Group 2, approximately 10% of patients not receiving a KP have a stable CB (within 10% of the starting CB) 12 weeks after diagnosis based on historical data (null hypothesis). We are interested in determining whether PTX can increase this to 30% of patients (alternative hypothesis), which would be a large enough response to make the medication worth pursuing in a larger Phase 3 trial. To test the null hypothesis versus the alternative hypothesis at a significance level of 0.05 and power of 80%, 25 patients must be enrolled. Of these 25, 6 or more patients must respond to reject the null hypothesis. Furthermore, the study will be terminated early if, of the first 15 patients, fewer than 2 respond.



G. Ethical Issues

i) Informed consent

Participants will only be enrolled after their parents understand the nature and objectives of the trial, as well as the attendant risks and possible discomforts. All families will be given a consent form describing PTX and possible side-effects (see Consent in appendix).

ii) Children as research subjects

PTX may benefit patients with BA by reducing progression of the disease. This study does have risks. PTX has been studied extensively in pediatric populations and is commonly associated with emesis. However, it has never been found to cause any serious adverse events in children. This study also involves blood draws. However, these blood draws are part of routine clinical care, and would be performed independent of participation in this trial.

H. Pharmaceutical Information

i) Formulation – 20 mg/ml compounded from 400 mg tablets by Texas Children's Hospital Pharmacy

ii) Storage – Store opened bottles at 4°C for 1 month

iii) Administration – Orally with needleless syringe in sides of mouth

iv) Toxicities

PTX is a methylxanthine derivative, belonging to the same family of molecules as caffeine. It has been widely studied in septic neonates as well as adults with liver disease, and no serious adverse effects have been reported. In the neonatal studies, PTX was well-tolerated and no patients were withdrawn because of side-effects.[11]

The PTX side-effect profile also has been reported in children ages 6 months to 5 years taking 20 mg/kg/day orally for Kawasaki disease.[14] Fifteen of 24 patients reported mild to moderate adverse events that may or may not have been related to PTX, and none had to discontinue the medication. The adverse events included vomiting/spitting out immediately after dosing (11 episodes in 7 patients) and abdominal pain (6 episodes in 3 patients). Eight patients reported 14 non-gastrointestinal events, including mild cough, inability to walk without help, I/VI systolic flow murmur anemia, clear rhinorrhea, diaper rash, irritability, and temporary hearing loss. No dose-limiting, unusual, or idiosyncratic reactions were observed in this study.

In addition, in adult studies, PTX does lead to vomiting and epigastric discomfort in less than 1% of patients. These symptoms were reversed when the medication was stopped.[8] In adults, PTX was also trialed peri-operatively with no excess serious side-effects compared to controls.[9] A summary of the side-effect profile is as follows:

>10% of patients	vomiting and abdominal pain
<10% of patients	mild cough, runny nose, diaper rash, irritability, low red blood cell count (anemia), heart murmur, difficulty moving limbs, and temporary hearing loss
<1% of patients	allergic reaction

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J. Appendix

i) Data Safety Monitoring Plan

ii) Consent

Data Safety Monitoring Plan

The PI and other co-investigators listed in the protocol are responsible for data safety and monitoring.

I. Monitoring

The PI and study staff will monitor for adverse events (AE) on a subject-by-subject basis, continuously for the 12 week course of therapy. AE will be detected in multiple ways:

- self-reported by parents
- reported by parents during the 2, 4, 8, or 12 week follow-up clinic visit
- clinical exam during the 2, 4, 8, or 12 week follow-up
- scheduled laboratory tests (serum liver panel, complete blood count, coagulation profile, chemistry, pre-albumin, and Vitamin D level)
- scheduled abdominal ultrasounds

Two types of AEs will be monitored: (1) those related to the normal progression of BA, and (2) those specific to PTX:

(1) AEs related to the progression of BA include: elevated liver function tests, abnormal coagulation tests, hyperkalemia/acidosis, neutropenia, lymphopenia, thrombocytopenia, hepatosplenomegaly, ascites, cholangitis, failure to thrive, steatorrhea, diaper rash, increased jaundice/icterus, acholic stools, and end-stage liver disease.

(2) AEs related to PTX, as previously reported, include: vomiting/spitting out medications, abdominal discomfort, cough, anemia with new heart murmur, rhinorrhea, diaper rash, irritability, and temporary hearing loss.

All AEs will be graded as follows:

AE grading and attribution scale

0 = No adverse event or within normal limits

1 = Mild AE, not requiring treatment

2 = Moderate AE, resolved with treatment

3 = Severe AE, resulted in inability to carry on normal activities and required professional medical attention

4 = Life-threatening or disabling AE

5 = Fatal AE

II. Reporting

To avoid any conflict of interest, the PI and/or study coordinator will report all AEs to the IRB following the schedule below. The PI will also report AEs to all staff members using the same schedule.

Schedule of AE reporting (all on a subject-by-subject basis)

Grade 1-4 AEs typically seen in BA	*Report after 12 weeks of therapy to IRB*
Grade 1-4 AEs not typically seen in BA	*Report within 14 days to IRB*

All Grade 5 AEs	*Report within 7 days to IRB*
All subjects withdrawing from study	*Report within 7 days to IRB*
Other unintended protocol deviations	*Report within 14 days to IRB*

III. Stopping Rules

1. In Group 1, the study will be terminated if 9 of the first 13 subjects do not respond to PTX therapy (negative outcome).
2. In Group 1, the study will be terminated if the first 26 subjects do respond (positive outcome).
3. In Group 2, the study will be terminated if 2 of the first 15 subjects do not respond to PTX therapy (negative outcome).
4. In Group 2, the study will be terminated if the first 6 subjects do respond (positive outcome).
5. In both groups, the study will be terminated if multiple unanticipated serious AEs occur from PTX therapy. This decision will be made in conjunction with the IRB.

CONSENT FORM
Institutional Review Board for Baylor College of Medicine and Affiliated Hospitals
Pentoxifylline in Biliary Atresia

H-31387 - PENTOXIFYLLINE THERAPY IN BILIARY ATRESIA

Background

You are invited to take part in a research study, to determine whether the medication PENTOXIFYLLINE reduces liver damage in BILIARY ATRESIA.

Please read this information and feel free to ask any questions before you agree to take part in the study.

WHAT IS BILIARY ATRESIA?

Biliary atresia is a serious liver disease that affects infants. Approximately 1 in every 10,000 infants has the disease. We do not know why some infants have the disease while others do not.

Biliary atresia occurs when narrow tubes called bile ducts become blocked. Normally, the liver sends liquids to the intestines through bile ducts. One liquid the liver sends is called bile. Bile is a strong chemical that digests the fats we eat.

In biliary atresia, the bile duct becomes blocked. Bile can no longer pass through to the intestines. Instead, bile stays in the liver. Bile starts digesting the liver and over time causes liver damage.

In order to live, we need our liver to work properly. In biliary atresia, the liver becomes damaged and stops working properly. Biliary atresia causes death if it is not treated.

HOW IS BILIARY ATRESIA TREATED?

Right now we have not discovered medicines for biliary atresia. We only have surgeries that can help your child.

The first surgery is called the Kasai operation. It has two steps: (1) first, surgeons remove the blocked bile duct, and (2) second, surgeons connect the liver directly to the intestines. In this way, the liver may be able to send bile directly to the intestine.

The Kasai operation does not always work. Also, the Kasai operation does not work in older infants, so your doctor may decide not to perform the operation at all.

Liver transplant is the second surgery available. We use liver transplant if the Kasai operation does not work. We also use liver transplant if an infant is too old for the Kasai operation.

WHAT IS PENTOXIFYLLINE?

We are now testing a medication that may help biliary atresia. The medicine is called pentoxifylline. Pentoxifylline belongs to the same group of medications as caffeine.

Pentoxifylline has never been tried in biliary atresia. It has been used in adults with other liver diseases. In adults, pentoxifylline seems to slow down liver scarring. It also seems to help the liver repair itself.

Pentoxifylline has been used in children for other diseases. It has been used safely in newborns with serious infections. It has also been used safely in children with diseases of their immune system.

HOW WILL WE KNOW IF PENTOXIFYLLINE WORKS?

We think pentoxifylline may help in biliary atresia. We think that pentoxifylline could reduce liver damage.

In biliary atresia, doctors use many tests to look for liver damage. They weigh children to see if they lost weight. They draw liver blood tests to see if they are worse. They use ultrasound to measure the size of the liver and other organs.

In this study, we will use results from these tests to see if pentoxifylline reduces liver damage. The test we are most interested in is the "conjugated bilirubin." If pentoxifylline works, it should improve the "conjugated bilirubin" levels.

Purpose

This research aims to determine whether pentoxifylline reduces liver damage in biliary atresia. We will use "conjugated bilirubin" levels as the main indicator of liver damage.

Procedures

The research will be conducted at the following location(s): Baylor College of Medicine, TCH: Texas Children's Hospital.

If you decide to participate, your child will take pentoxifylline by mouth 3 times every day, for a total of 12 weeks. For each dose, you will need to measure the correct amount of pentoxifylline liquid using a needleless syringe. You will then need to place the needleless syringe in your child's mouth and give the medication.

You will also need to keep a daily diary. In this diary, you will record the times you gave pentoxifylline. You will also record any concerns you have about the medication. If you think the medication is causing a side-effect, you will write it here and then call the on-call research team.

Pentoxifylline will be supplied to you free-of-charge. We will pay for the medications using hospital funds and grants from private foundations. The drug company is not involved in this study.

Pentoxifylline will be prepared by the Texas Children's Hospital pharmacy. They will make it by crushing a tablet and mixing it in liquid. Each bottle of medication can be used for 4 weeks, so you will need to pick up a new bottle at the 4 and 8 week clinic visits.

Taking pentoxifylline will be the only difference in your child's care. Your child otherwise will be treated exactly like all other patients with biliary atresia. Your child will not require any extra tests or office visits for participating in this study. To determine if pentoxifylline works, we will use the results in your child's electronic medical chart that are recorded during routine clinical care.

Your child will receive standard care for biliary atresia, even if you decide not to participate in this study. This includes but is not limited to the following:

1. DIAGNOSIS OF BILIARY ATRESIA

This occurs before the study starts. It will be done by your doctor. It involves blood tests, radiology tests, and/or a liver biopsy. Your doctor will have a separate consent form for the liver biopsy.

2. BASELINE TESTS BEFORE STARTING PENTOXIFYLLINE

These tests are performed on all infants with biliary atresia, even if they are not part of the study. They include:
a) A weight measurement, to monitor growth.
b) Blood tests, including liver panel, complete blood cell count, coagulation profile, chemistry panel, pre-albumin, and Vitamin D measurements. The liver panel includes a "conjugated bilirubin" level.
c) An ultrasound to measure liver and spleen size.

3. START PENTOXIFYLLINE

While you are still in the hospital, the research team will give you the medication to give to your child. You will not need to go to the pharmacy to pick up the first bottle. The research team will also help you give the first doses of the medication to your child.

If your child receives the Kasai operation, you will start giving the medication when your surgeons think your child is ready (approximately 3-5 days after the operation). If your child does not receive the Kasai operation, you will start giving the medication immediately.

4. ROUTINE SCHEDULED CLINIC VISITS

These visits will be at approximately 2, 4, 8, and 12 weeks after discharge from the hospital. In these visits, your child will receive standard clinical care by their doctor. This includes a weight measurement and physical exam.

You and your doctor will also discuss your diary, as well as any pentoxifylline side-effects that you are concerned about. At this time, your doctor will also increase the pentoxifylline dose if your child has gained weight.

5. ROUTINE SCHEDULED BLOOD TESTS

Your child will have routine blood tests at every clinic visit. These tests are performed on all patients with biliary atresia. They included liver panel, complete blood cell count, coagulation profile, chemistry panel, and pre-albumin measurements.

6. WEEK 12 CLINIC VISIT

On this visit, pentoxifylline will be stopped. In addition, your child will have two additional tests: a blood test for Vitamin D levels, and an ultrasound to measure liver and spleen size. These tests are normally performed at the 12 week visit for all patients with biliary atresia.

After the week 12 clinic visit, you and your child will continue follow-up with your doctor. You and your doctor will determine the appropriate follow-up schedule at that time.

7. OTHER INFORMATION

It is very important that you make all scheduled clinic visits to receive routine clinical care. If your child misses a clinic visit or blood test, your child can still participate in the study. However, your child must continue taking pentoxifylline for the 12 week period and must have a "conjugated bilirubin" blood test at the 12 week visit.

*** IMPORTANT NUMBERS ***

The Primary Investigator for this study is Sanjiv Harpavat, MD PhD. He cares for children with liver disease and is your doctor's colleague. He can be reached at 832-824-2099 Pager #2144.

If you have any concerns about side-effects, you can call your doctor or Dr. Harpavat. If you need immediate assistance after-hours, you can call the 24-hour on-call service at 832-824-2099 and ask for "Gastroenterology On-Call."

For the blood tests, we will require blood from your child. The approximate amount of blood is as follows: three quarters of a teaspoon (3.75 milliliters) for the baseline tests; one half of a teaspoon (2.5 milliliters) each for the weeks 2, 4, and 8 tests; and three quarters of a teaspoon (3.75 milliliters) for the week 12 tests.

Potential Risks and Discomforts

Pentoxifylline has been tested in two groups of children. The first group is newborns with serious infections. The second is children 6 months to 5 years old. In these groups, pentoxifylline did not cause any serious side effects. Pentoxifylline has never been tested in children between 0 and 6 months old.

Pentoxifylline in these and other studies has been associated with the following side-effects: >10% of patients may have vomiting and abdominal pain; an unknown number of patients may also develop increased cholesterol levels, abdominal cramps, abdominal pain, anorexia, constipation, dyspepsia, flatulence, heartburn, nausea, vomiting, or leucopenia.

A member of the study team will always be available to answer any questions about side-effects.

There may be unknown risks or discomforts involved. Study staff will update you in a timely way on any new information that may affect your decision to stay in the study.

Potential Benefits

The benefits of participating in this study may be: improved vitamin levels. However, you may receive no benefit from participating.

Alternatives

You may choose to not participate in this study.

Subject withdrawal from a study

If Chenodal causes side-effects in your child, you may withdraw your child from the study at any time.

Subject Costs and Payments

You will not be asked to pay any costs related to this research.

You will not be paid for taking part in this study.

Research related Injury

If your child has side-effects, we will treat them. The most common side effect is elevated liver enzymes (above starting levels) and/or diarrhea (above starting levels). If either of these symptoms occur, we will reduce the dose of the medication. If either symptoms persists, we will stop the medication.

Research personnel will try to reduce, control, and treat any complications from this research. If you are injured because of this study, you will receive medical care that you or your insurance will have to pay for just like any other medical care.

Subject's Rights

Your signature on this consent form means that you have received the information about this study and that you agree to volunteer for this research study.

You will be given a copy of this signed form to keep. You are not giving up any of your rights by signing this form. Even after you have signed this form, you may change your mind at any time. Please contact the study staff if you decide to stop taking part in this study.

If you choose not to take part in the research or if you decide to stop taking part later, your benefits and services will stay the same as before this study was discussed with you. You will not lose these benefits, services, or rights.

Your Health Information

We may be collecting health information that could be linked to you (protected health information). This protected health information might have your name, address, social security number or something else that identifies you attached to it. Federal law wants us to get your permission to use your protected health information for this study. Your signature on this form means that you give us

permission to use your protected health information for this research study.

If you decide to take part in the study, your protected health information will not be given out except as allowed by law or as described in this form. Everyone working with your protected health information will work to keep this information private. The results of the data from the study may be published. However, you will not be identified by name.

People who give medical care and ensure quality from the institutions where the research is being done, the sponsor(s) listed in the sections above, representatives of the sponsor, agents of the Food and Drug Administration, and regulatory agencies such as the U.S. Department of Health and Human Services will be allowed to look at sections of your medical and research records related to this study. Because of the need for the investigator and study staff to release information to these parties, complete privacy cannot be guaranteed.

The people listed above will be able to access your information for as long as they need to, even after the study is completed.

If you decide to stop taking part in the study or if you are removed from the study, you may decide that you no longer allow protected health information that identifies you to be used in this research study. Contact the study staff to tell them of this decision, and they will give you an address so that you can inform the investigator in writing. The investigator will honor your decision unless not being able to use your identifiable health information would affect the safety or quality of the research study.

The investigator, SANJIV HARPAVAT, and/or someone he/she appoints in his/her place will try to answer all of your questions. If you have questions or concerns at any time, or if you need to report an injury related to the research, you may speak with a member of the study staff: For any emergencies, please go directly to the Emergency Room. For other issues, during the day or night, please call SANJIV HARPAVAT at 832-824-2099 Pager #2144. If unavailable, then call GI FELLOW ON-CALL at 832-824-2099.

Members of the Institutional Review Board for Baylor College of Medicine and Affiliated Hospitals (IRB) can also answer your questions and concerns about your rights as a research subject. The IRB office number is (713) 798-6970. Call the IRB office if you would like to speak to a person independent of the investigator and research staff for complaints about the research, if you cannot reach the research staff, or if you wish to talk to someone other than the research staff.
