HRP-503B – BIOMEDICAL RESEARCH PROTOCOL
(2016-1)

Protocol Title: An Efficacy Trial of low dose All-trans Retinoic Acid (ATRA) in Patients with Primary Sclerosing Cholangitis

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Version Date: 9/17/2018

(*If applicable*) Clinicaltrials.gov Registration #: Pending

INSTRUCTIONS
This template is intended to help investigators prepare a protocol that includes all of the necessary information needed by the IRB to determine whether a study meets approval criteria. Read the following instructions before proceeding: 1. Use this protocol template for a PI initiated study that includes direct interactions with research subjects. Additional templates for other types of research protocols are available in the system Library. 2. If a section or question does not apply to your research study, type "Not Applicable" underneath. 3. Once completed, upload your protocol in the "Basic Information" screen in IRES IRB system.

SECTION I: RESEARCH PLAN

1. Statement of Purpose: State the scientific aim(s) of the study, or the hypotheses to be tested.

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The purpose of this research study is to determine whether a low dose of ATRA will improve laboratory tests of liver and bile duct inflammation in patients with PSC. We will also look for changes to other blood tests which are related to inflammation, scarring, and the immune system.

2. Probable Duration of Project: State the expected duration of the project, including all follow-up and data analysis activities.
   3 years for data collection; 3 -5 additional years for analysis.

3. Background: Describe the background information that led to the plan for this project. Provide references to support the expectation of obtaining useful scientific data.
   Primary Sclerosing Cholangitis is an orphan chronic cholestatic liver disease for which there is no accepted therapy. The disease generally progresses over a period of 1-15 years, ultimately resulting in liver failure and the need for liver transplant or cancer (cholangiocarcinoma, colon cancer, gallbladder cancer). Therefore, there is an urgent need to develop novel therapeutic options.

   Studies from our laboratory and clinics on cholestasis have led to key observations that provide the scientific rationale for this specific clinical efficacy trial.

   1) *All-trans retinoic acid is a potent inhibitor of CYP7A1 in isolated human and rodent hepatocytes and reduces the bile acid pool size by 50% in bile duct ligated rat model of cholestasis resulting in significant reductions in liver injury* (4-5).

   2) *Studies with ATRA administration to patients with PSC confirm that ATRA inhibits CYP7A1* (6). This was observed through a Human Pilot studying the combination of ATRA and UDCA conducted at Yale and Mayo Clinics (HIC 1012007734). However, the full dose of ATRA, which is already in clinical use and FDA approved for management of acute promyelocytic leukemia, resulted in frequent side effects such as self-limited headaches and this indicates the need to evaluate efficacy of ATRA in patients with PSC while using lower doses.

   Bibliography

   1. *Allen et al. AJP 178:175, 2011.*
   2. *Cai SY et al. Hepatology 60:300A, 2014.*
   3. *Cat SY et al. 62:610A, 2015.*
   4. *Cai SY et al. J.Lipid Res 51:2265, 2010.*
   5. *He et al. Hepatology 53:548, 2011.*
   6. *Assis DN et al.* J Clin Gastroenterol. 51: e11-e16, 2017.

4. Research Plan: Summarize the study design and research procedures using non-technical language that can be readily understood by someone outside the discipline. Be sure to distinguish between standard of care vs. research procedures when applicable, and include any flowcharts of visits specifying their individual times and lengths. Describe the setting in which the research will take place.

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We propose an investigator-initiated efficacy trial of low dose ATRA monotherapy in a small group of patients with PSC to be conducted at the Yale Liver Clinics.

Study Design for an efficacy trial of low dose All-Trans Retinoic Acid (ATRA)in Primary Sclerosing Cholangitis (PSC)

I. Objective: Evaluate effects of low dose ATRA therapy on serum alkaline phosphatase (ALP) over 24 weeks in adults with PSC.

II. Study Design: Single-arm, open label study in PSC, comparing pre-treatment and post-treatment serum ALP levels in individual subjects and as a group.

III. Number of Subjects: Goal of enrolling 20 adult subjects with PSC.

IV. Dosage and Administration: ATRA 10 mg tablets will be taken with food once daily for 3 days and then increase to twice daily for the remainder of the study. With an option to dose escalate to 20 mg twice daily if Alk Phos does not reduce 5% or more after the first 12 weeks.

V. Efficacy Evaluation
- Primary Endpoint: Percent change of serum ALP from baseline to week 24
- Other Endpoints: The percent of patient who have the following from baseline to weeks 12 and 24, normalization of ALP, ALP < 1.5 x ULN and 50% reduction, reduction in C4, serum bile acids, ALT and serum ELF score improvement in fibrosis per Transient Elastography by at least 1 stage .

VI. Safety Evaluation
- Evaluate safety of ATRA with respect to frequency and severity of adverse events.

VII. Facilities and Equipment
- ATRA will be stored and dispensed for the study through the Yale New Haven Hospital Research Pharmacy.
- Enrollment for the study will occur at the Yale Liver Center Clinics, 40 Temple St Suite 1A as well as the Yale Church Street Research Unit the CSRU.
- Study visits will occur at the Yale Liver Center Clinics, 40 Temple St Suite 1A as well as the Yale Church Street Research Unit the CSRU.
- Blood samples and research analyses will be stored and tested at the Yale Liver Center research building (TAC).
- Clinical labs will be performed as per standard lab testing at the Yale New Haven laboratories.

VIII. Screening Treatment and Follow up Visits

All below procedures are research related not standard of care.
- Screening will be within 6 weeks of the Baseline Visit.
- Subjects will be seen in clinic for screening, on treatment weeks 1, 4 and 12, end of treatment week 24, and follow up week 28.
- Phone calls will be made to the patient on weeks 8 and 16.
- If after week 12 the Alk Phos has not reduced 5% or more the dose will be doubled, and the wk 16 phone call will be replaced with an additional clinic visit.

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- Approximately 60 mL or 4 tablespoons of blood will be drawn at each of the above clinic visits and again at week 48.
- Clinical Lab Testing: Serum ALP, total/direct bilirubin, AST, ALT, GGT, albumin, serum bile acids, lipid panel, basic metabolic panel, CBC, PT/INR.
- Research Lab Testing: Serum C4, MCP-1, IL-8, serum ELF.
- Additionally, blood will be stored in a de-identified way in order to perform potential genetic and other tests to understand the risks factors for the development of PSC.
- Imaging: Transient Elastography (Fibroscan) at Baseline Visit, and week 24.
- Complete and symptom based physical examinations and quality of life questionaries will be performed at each visit.
- Symptoms will also be assessed by phone at weeks 8 and 16.
- If at any point the Bilirubin, Alk Phos, AST or ALT increases 1.5 x over the patients baseline value, the ATRA will be held for 2 weeks. After 2 weeks the labs will be retested, and if the value is under 1.5 x the patients baseline value ATRA will be restarted at the same dose. If the value remains over 1.5 x the patients baseline value after 2 weeks the patient will be discontinued from the study treatment.

The screening and end of treatment visit (week 24) will take about 30-40 minutes, the on treatment visits (weeks 1, 4 , 12) and follow up 1 (week 28) will take about 20-30 minutes, follow up 2 (week 48) will take about 10 minutes, and the phone calls on week 8 and 16 will take about 10 minutes.

Women of childbearing age will need to use two forms of contraception, and have a negative pregnancy tests at screening and every study visit. A total of 6 pregnancy tests will be taken which will be paid for and provided by the research study.

5. Genetic Testing N/A ☐

A. Describe

i. the types of future research to be conducted using the materials, specifying if immortalization of cell lines, whole exome or genome sequencing, genome wide association studies, or animal studies are planned There is the potential for the banked specimens to be used for immortalization of cell lines, whole exome or genome sequencing, genome wide association studies, and animal studies.

ii. the plan for the collection of material or the conditions under which material will be received blood samples will be collected by a trained phlebotomist.

iii. the types of information about the donor/individual contributors that will be entered into a database We will use oncore.ynhh.org for the patient's information. Oncore will hold all of the current study data, and if samples are stored for future use. We will also use Epic for appropriate documentation.

iv. the methods to uphold confidentiality The study personal will use oncore with encrypted laptops or university computers.

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B. What are the conditions or procedures for sharing of materials and/or distributing for future research projects? The genetic material collected from the blood samples for future research projects may be shared within the network of physicians who have a professional working relationship with the PI and SubIs.
C. Is widespread sharing of materials planned? No
D. When and under what conditions will materials be stripped of all identifiers? Once the blood has been aliquoted into cryovials for storage no identifying information will be present. The link between the numerical code and the patient identifying information will be stored in oncore and relevant epic documentation only.
E. Can donor-subjects withdraw their materials at any time, and/or withdraw the identifiers that connect them to their materials? No. If the subject withdraws from the study after samples have been collected, the researchers may continue to use those samples, however, no future samples will be collected from the subject after they withdraw.
    i. How will requests to withdraw materials be handled (e.g., material no longer identified: that is, de-identified) or material destroyed)? To withdraw from the study, the participant can call a member of the research team at any time and inform them of their intent to be removed. There will be no change to their medical treatment based on the decision to participate or not participate. The samples already collected will remain in storage, and no future samples will be collected.
F. Describe the provisions for protection of participant privacy We will use oncore.ynhh.org which will be accessed using encrypted laptops or Yale computers. All research records will be stored on either Yale provided Ironkey flash drives or in locked cabinets, access to identified data will be limited and the importance of confidentiality will be continuously impressed on the research team. The association between the code created after the samples are received and patient identity will be stored only in oncore and relevant Epic documentation. Once all data is collected, the data may be matched using the subject number and any identifiers will be removed from the data. All informed consent documents will be kept in a secure location separate from the data and electronically in Oncore and the patients chart in Epic.
G. Describe the methods for the security of storage and sharing of materials Samples will be stored in a key-locked negative 80^{o} C freezer. De-identified sample storage and data storage methods for security are detailed in Section IV (Protection of Research Subjects; Confidentiality & Security of Data). Data collected by the Principal Investigator and other researchers listed on this protocol may be used for additional research purposes by the network of physicians who have a professional working relationship with the PI and SubIs.

6. Subject Population: Provide a detailed description of the types of human subjects who will be recruited into this study.
   Male and female patients ages 18-80 with PSC, seen at the Yale Liver and Research Clinics.

7. Subject classification: Check off all classifications of subjects that will be <u>specifically recruited for enrollment</u> in the research project. Will subjects who may require additional safeguards or other considerations be enrolled in the study? If so, identify the population of subjects requiring special safeguards and provide a justification for their involvement.

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☐Children	☐ Healthy	☐Fetal material, placenta, or dead fetus
☒Non-English Speaking	☐ Prisoners	☐Economically disadvantaged persons
☐Decisionally Impaired	☐ Employees	☐Pregnant women and/or fetuses
☐Yale Students	☒ Females of childbearing potential	

NOTE: Is this research proposal designed to enroll children who are wards of the state as potential subjects?

Yes ☐ No ☒

8. Inclusion/Exclusion Criteria: What are the criteria used to determine subject inclusion or exclusion?

Inclusion Criteria

- Males and females ages 18-80
- Diagnosis of large-duct PSC based on ERCP or MRCP, or liver biopsy findings without alternative explanation for findings, for at least 6 months.
- Serum ALP levels persistently more than 1.5 x upper limit of normal over the past 6 months.
- Ursodeoxycholic acid therapy must be discontinued for at least 3 months.
- At least 2 forms of barrier protection for males and females of child-bearing age.

Exclusion Criteria

- Small duct PSC, overlap with autoimmune hepatitis, IgG4 disease or secondary sclerosing cholangitis.
- History of cancer in the preceding 5 years, except adequately treated non-melanoma skin cancer, carcinoma in situ of the cervix, in situ prostate cancer.
- Viral hepatitis including hepatitis A, B, C, D, E.
- Decompensated cirrhosis, or planned liver transplantation.
- Recent diagnostic or therapeutic biliary manipulation (endoscopic, radiologic) within the past 3 months.
- Ascending Cholangitis requiring antibiotics within the past 3 months.
- Uncontrolled IBD, or IBD requiring the use of steroids.
- Acute or Chronic Kidney Disease with serum creatinine > 2 mg/dL.
- Allergy to ATRA or vitamin A compounds.

9. How will eligibility be determined, and by whom? Write here

The principal investigators, sub-investigators and/or delegates under their direct supervision will determine eligibility in accordance with the requirements of the protocol.

10. Risks: Describe the reasonably foreseeable risks, including risks to subject privacy, discomforts, or inconveniences associated with subjects participating in the research.

The medication ATRA has been associated with possible side effects in patients who have leukemia and who take the drug orally for that disease. These side effects include:

- Chest discomfort – up to 32% of patients.
- Abnormal heart rhythms – up to 23% of patients.

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Both chest discomfort and abnormal heart rhythms are adverse reaction listed for tretinoin (a related form of ATRA). The symptoms will be monitored by the treating physician by asking the patient if they are having chest discomfort or irregular heartbeats. Additional protocol specific monitoring should not be needed, however if a patient is experiencing symptoms an evaluation including an EKG will be pursued and the appropriate CTCAE term and grade will be documented in the patient's chart.

- Increased triglyceride levels – up to 60% of patients.
- Dry skin – up to 77% of patients.
- Nausea – up to 57% of patients.
- Weight gain – up to 23% of patients.
- Retinoic Acid Syndrome – a specific series of symptoms in patients with leukemia who are taking ATRA, in up to 75% of patients taking the drug for that specific disease. Symptoms include fever, shortness of breath, weight gain, increased white blood cell count, and fluid accumulation around the lungs and heart. This typically occurs within the first month of treatment.
- Liver Test Increase – a mild increase in liver tests has been found in up to 60% of patients taking ATRA for leukemia.
- Dizziness – up to 20% of patients.
- Headache – up to 86% of patients.
- Infections – up to 58% of patients.
- Risk of fetal malformations – ATRA is a pregnancy category D medication. There is a high risk of birth defects in babies born to mothers taking ATRA. Therefore, ATRA should not be used during pregnancy. If ATRA is used by a child-bearing aged mother, a negative pregnancy tests should be performed before taking the drug. A pregnancy test should also be done at every study visit. Two forms of contraception should be used while taking the drug, and for the month following discontinuation of the drug. Pregnancy should not be planned for up to 6 months after stopping the medication. Treatment should be stopped immediately if pregnancy develops.

Other than the pregnancy risks described above, it is not known if these side effects are seen as often or at all in patients who do not have leukemia and who have liver conditions such as PSC.

For those who develop headaches from ATRA, this symptom goes away within a few days for the majority of patients. If the subject experience a significant headache or similar symptom, but are otherwise healthy and still able to participate, we will reduce the dose of your medication so that you can tolerate the medication more easily.

In our previous Pilot of ATRA and UDCA in PSC the following frequency of adverse effects was observed as reported below (6). None were grade 3 or above:

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TABLE 2. Reported Adverse Effects

Adverse Effects	Frequency (%)
Headache	63
Tinnitus	26
Diarrhea	16
Dry skin/mucus membranes	10
Myalgia	5
Anemia	5

Privacy risks are always a potential risk of a clinical study, but will be minimized by stringent procedures to ensure compliance with local and federal regulations regarding protected health information. We do not believe that this study poses an elevated risk for breach of subject privacy.

We do not believe subjects participating in the study will suffer from significant inconveniences, since they are currently under treatment by physicians at Yale, and thus are presenting to their usual centers of care, at which the study will be conducted.

11. Minimizing Risks: Describe the manner in which the above-mentioned risks will be minimized.
Close clinical monitoring of participating subjects will be implemented as per study protocol, including monthly assessments (at clinic or by phone) and scheduled lab work for all subjects. If there is any evidence of adverse effects from medications or change in the clinical condition, subjects will be asked to return to the clinic for evaluation and further testing.
Chest discomfort and abnormal heart rhythms will be monitored by the treating physician by asking the patient if they are having chest discomfort or irregular heartbeats, if a patient is experiencing symptoms an evaluation including an EKG will be pursued and the appropriate CTCAE term and grade will be documented in the patient's chart.

12. Data and Safety Monitoring Plan: Include an appropriate Data and Safety Monitoring Plan (DSMP) based on the investigator's risk assessment stated below. (Note: the HIC will make the final determination of the risk to subjects.)
    a. What is the investigator's assessment of the overall risk level for subjects participating in this study? ii. Greater than minimal
    b. If children are involved, what is the investigator's assessment of the overall risk level for the children participating in this study? NA
    c. Include an appropriate Data and Safety Monitoring Plan. Examples of DSMPs are available here http://your.yale.edu/policies-procedures/forms/420-fr-01-data-and-safety-monitoring-plans-templates for
        i. Minimal risk
        ii. Greater than minimal
    d. For multi-site studies for which the Yale PI serves as the lead investigator: NA
        i. How will adverse events and unanticipated problems involving risks to subjects or others be reported, reviewed and managed? NA
        ii. What provisions are in place for management of interim results? NA
        iii. What will the multi-site process be for protocol modifications? NA

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Greater Than Minimal Risk DSMP

1. Personnel responsible for the safety review and its frequency:

The principal investigators will be responsible for monitoring the data, assuring protocol compliance, and conducting the safety reviews at the specified frequency, which must be conducted at a minimum of every 6 months (including when reapproval of the protocol is sought). During the review process, the principal investigators (monitors) will evaluate whether the study should continue unchanged, require modification/amendment, or close to enrollment. Either the principal investigators or the IRB have the authority to stop or suspend the study or require modifications.

2. The risks associated with the current study are deemed greater than minimal for the following reasons: (choose those that apply)

1. We do not view the risks associated with the ingestion of ATRA as minimal risks.

Although we have assessed the proposed study as one of greater than minimal risk, the potential exists for anticipated and/or unanticipated adverse events, serious or otherwise, to occur since it is not possible to predict with certainty the absolute risk in any given individual or in advance of first-hand experience with the proposed study methods. Therefore, we provide a plan for monitoring the data and safety of the proposed study as follows:

3. Attribution of Adverse Events:

Adverse events will be monitored for each subject participating in the study and attributed to the study procedures / design by the principal investigator (*Insert Investigator Name*) according to the following categories:

a.) Definite: Adverse event is clearly related to investigational procedures(s)/agent(s).
b.) Probable: Adverse event is likely related to investigational procedures(s)/agent(s).
c.) Possible: Adverse event may be related to investigational procedures(s)/agent(s).
d.) Unlikely: Adverse event is likely not to be related to the investigational procedures(s)/agent(s).
e.) Unrelated: Adverse event is clearly not related to investigational procedures(s)/agent(s).

4. Plan for Grading Adverse Events:

In this study we will follow the Common Terminology Criteria for Adverse Events (CTCAE) version 4 grading system as follows:

Grade 1 -- Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
Grade 2 -- Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental activities of daily living (ADL)*.

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Grade 3 -- Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self care ADL**.
Grade 4 -- Life-threatening consequences; urgent intervention indicated.
Grade 5 -- Death related to AE.

*Instrumental ADL refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.
**Self care ADL refer to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.

5. Plan for Determining Seriousness of Adverse Events:

Serious Adverse Events:

In addition to grading the adverse event, the principal investigators will determine whether the adverse event meets the criteria for a Serious Adverse Event (SAE). An adverse event is considered serious if it results in any of the following outcomes:

1. Death;
2. A life-threatening experience in-patient hospitalization or prolongation of existing hospitalization;
3. A persistent or significant disability or incapacity;
4. A congenital anomaly or birth defect; OR
5. Any other adverse event that, based upon appropriate medical judgment, may jeopardize the subject's health and may require medical or surgical intervention to prevent one of the other outcomes listed in this definition.

An adverse event may be graded as severe but still not meet the criteria for a Serious Adverse Event. Similarly, an adverse event may be graded as moderate but still meet the criteria for an SAE. It is important for the PI to consider the grade of the event as well as its "seriousness" when determining whether reporting to the IRB is necessary.

6. Plan for reporting UPIRSOs (including Adverse Events) to the IRB

The principal investigators will report the following types of events to the IRB:

Any incident, experience or outcome that meets ALL 3 of the following criteria:

1. Is unexpected (in terms of nature, specificity, severity, or frequency) given (a) the research procedures described in the protocol-related documents, such as the IRB-approved protocol and informed consent document and (b) the characteristics of the subject population being studied; AND
2. Is related or possibly related to participation in the research (*possibly related* means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research); AND

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3. Suggests that the research places subjects or others at greater risk of harm (including physical, psychological, economic, legal, or social harm) than was previously known or recognized.

Unanticipated Problems Involving Risks to Subjects or Others (UPIRSOs) may be medical or non-medical in nature, and include – but are not limited to – *serious, unexpected, and related adverse events* and *unanticipated adverse device effects*. ***Please note*** that adverse events are reportable to the IRB as UPIRSOs **only** if they meet all 3 criteria listed above.

These UPIRSOs/SAEs will be reported to the IRB in accordance with IRB Policy 710, using the appropriate forms found on the website. All related events involving risk but not meeting the *prompt* reporting requirements described in IRB Policy 710 should be reported to the IRB in summary form at the time of continuing review. If appropriate, such summary may be a simple brief statement that events have occurred at the expected frequency and level of severity as previously documented. In lieu of a summary of external events, a current DSMB report can be submitted for research studies that are subject to oversight by a DSMB (or other monitoring entity that is monitoring the study on behalf of an industry sponsor).

7. Plan for reporting adverse events to co-investigators on the study, as appropriate the protocol's research monitor(s), e.g., industrial sponsor, Yale Cancer Center Data and Safety Monitoring Committee (DSMC), Protocol Review Committee (PRC), DSMBs, study sponsors, funding and regulatory agencies, and regulatory and decision-making bodies.

For the current study, the following individuals, funding, and/or regulatory agencies will be notified (choose those that apply):

- ☒ All Co-Investigators listed on the protocol.
- ☐ Yale Cancer Center Data and Safety Monitoring Committee (DSMC)
- ☐ National Institutes of Health
- ☐ Food and Drug Administration (Physician-Sponsored IND #_____)
- ☐ Medical Research Foundation (Grant_____)
- ☐ Study Sponsor
- ☐ Other Data Safety Monitoring Board (DSMB) or Committee (DSMC)

The principal investigators will conduct a review of all adverse events upon completion of every study subject. The principal investigators will evaluate the frequency and severity of the adverse events and determine if modifications to the protocol or consent form are required.

For more guidance on Adverse Event reporting and DSMPs, see IRB Policy 710 Reporting Unanticipated Problems Involving Risks to Subjects or Others, including Adverse Events

13. Statistical Considerations: Describe the statistical analyses that support the study design.

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This is an exploratory Efficacy and Safety Human Pilot to determine if low dose ATRA is effective for reduction of cholestasis in patients with PSC and with a more favorable side effect profile with dose reduction. Although low dose ATRA monotherapy has not yet been studied in patients with PSC, we hypothesize a 30-40% reduction in serum Alkaline Phosphatase from baseline to week 24, which would require approximately 20 patients to achieve 90% power to detect a this difference at alpha of 0.05 using a two-sided one-sample t-test.

SECTION II: RESEARCH INVOLVING DRUGS, BIOLOGICS, RADIOTRACERS, PLACEBOS AND DEVICES

If this section (or one of its parts, A or B) is not applicable, check off N/A and delete the rest of the section.

A. RADIOTRACERS ☒N/A

1. Name of the radiotracer: *Write here*

2. Is the radiotracer FDA approved? ☐YES ☐NO

If NO, an FDA issued IND is required for the investigational use unless RDRC assumes oversight.

3. Check one: ☐IND# *Write here* or ☐RDRC oversight (RDRC approval will be required prior to use)

B. DRUGS/BIOLOGICS ☐N/A

1. If an exemption from IND filing requirements is sought for a clinical investigation of a drug product that is lawfully marketed in the United States, review the following categories and complete the category that applies (*and delete the inapplicable categories)*:

Exempt Category 1: The clinical investigation of a drug product that is lawfully marketed in the United States can be exempt from IND regulations if all of the following are yes:	
1. The intention of the investigation is NOT to report to the FDA as a well-controlled study in support of a new indication for use or to be used to support any other significant change in the labeling for the drug.	☒
2. The drug that is undergoing investigation is lawfully marketed as a prescription drug product, and the intention of the investigation is NOT to support a significant change in the advertising for the product.	☒
3. The investigation does NOT involve a route of administration or dosage level or use in populations or other factor that significantly increases the risks (or decreases the acceptability of the risks) associated with the use of the drug product	☒
4. The investigation will be conducted in compliance with the requirements for institutional (HIC) review and with the requirements for informed consent of the FDA regulations (21	☒

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CFR Part 50 and 21 CFR Part 56).	
5. The investigation will be conducted in compliance with the requirements regarding promotion and charging for investigational drugs.	☒

2. Background Information: Provide a description of previous human use, known risks, and data addressing dosage(s), interval(s), route(s) of administration, and any other factors that might influence risks. If this is the first time this drug is being administered to humans, include relevant data on animal models.

Please see investigator brochure pg 5-9

1. Nonclinical Studies

Studies by our group at Yale of ATRA in rats with cholestasis from common bile duct ligation have revealed a significant improvement in parameters of inflammation, necrosis, and fibrosis (1). Our results demonstrated that combination treatment with UDCA and ATRA significantly reduced bile salt pool size, liver fibrosis, necrosis, inflammation, and bile duct proliferation in the common bile duct ligated rat, an animal model of cholestasis. Furthermore, ATRA alone or in combination with UDCA repressed the expression of collagen 1A1 and MMP2 in primary human hepatic stellate cells, two key genes involved in liver fibrogenesis. Together, this data indicate that combination treatment with UDCA and ATRA is superior to UDCA treatment alone in these animal models of cholestasis, suggesting that ATRA mibht be a novel therapeutic approach for PSC and possibly other human cholestatic disorders.

Two week treatment (15 mg/kg body weight UDCA and 5 mg/kg all-trans RA by gavage daily) significantly improved liver gross appearance and histology in bile duct ligated cholestatic rats, including reduced bile duct proliferation, necrosis, inflammation and fibrosis. In addition, significant reductions in TNF-α, IL-1β and TGF-β1 mRNA expression were also detected in the livers receiving the combination treatment. Table 1 illustrates the profound effect of total hepatic bile salt and bile salt pool size. These results together with our results from human hepatocytes and hepatic stellate cells strongly suggest that the combination of RA and UDCA treatment might be beneficial for patients with PSC.

Table 1. ATRA +/- UDCA reduced hepatic bile salt levels and the bile salt pool size in BDL rats. Bile salt concentration/amount in rats.

	Sham-PBS (n=7)	BDL-PBS (n=7)	BDL-UDCA (n=5)	BDL-ATRA (n=6)	BDL-UDCA&ATRA (n=7)
Liver tissue (μmole/kg liver)	191.6±91.5	430.3±260.9	582.2±254.1	564.4±70.1	564±358.9
Bile cyst (mM)	N/A	15.79±5.14	16.30±4.44	23.00±8.00	**10.25±8.72[4]**
Bile cyst (μmole/kg body weight)	N/A	68.9±20.8	39.1±24.3[2]	35.6±24.7[2]	**11.3±9.4[2,3]**
Total hepatic bile salt (μmole/kg body weight)	5.58±2.67	94.79±19.92[1]	73.13±24.82[1]	61.78±24.68[1,2]	**40.29±19.81[1,2,3]**
Urine (mM)	0.02±0.02	1.22±1.15[1]	0.65±0.19[1]	0.51±0.68	0.52±0.41[1]

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Bile acid pool siz (µmole/kg body weight)	6.35±2.48	133.60±21.98[1]	112.49±28.94[1]	88.19±33.34[1,2]	**74.47±25.32[1,2,3]**

Note: p-value < 0.05 to Sham control[1], to BDL-PBS control[2], to UDCA treatment[3], and to ATRA treatment[4]. N/A, not applicable.

2. Effects in Humans

a. Pharmacokinetics and Product Metabolism in Humans

Please see (attached) package insert document for commercially available oral Tretinoin (Vesanoid trade name, Roche) for details of ATRA's attributes in humans.

b. Safety and Efficacy

Despite being generally well tolerated in clinical practice for patients with leukemia, there are several potential toxic effects of oral ATRA including hyperlipidemia, exacerbation of coronary artery disease and arrhythmias, teratogenicity (pregnancy category D), hyperleukocytosis (in leukemic patients), and increased liver function tests (3). A unique adverse event from ATRA in APL involves retinoic acid syndrome, caused by capillary leak from leukemic cells and can be induced by ATRA (7). This does not appear to be a potential toxic effect in patients without APL. In routine clinical practice hepatotoxicity while on ATRA is uncommon, though if this develops it appears to have a similar profile to that of vitamin A toxicity, and resolves with discontinuation of the drug (3,8). One case report describes severe hepatotoxicity attributed to ATRA in a patient receiving the drug for APL (9).

There is little published data on the use of oral ATRA for patients with liver disease. The study by Bocher *et al.* (5) from 2008 evaluated oral ATRA (dosed at 45 mg/m^2 per APL treatment recommendations) for 90 days in patients with hepatitis from chronic hepatitis C virus infection. Subjects in this study did not demonstrate elevations in their aminotransferase levels or develop other evidence of hepatotoxicity (or other serious adverse effects). In fact, levels of AST and ALT diminished in all patients. Based on this literature data, and the encouraging results of pre-clinical studies, initial human with oral ATRA for 90 days was justified for purposes of a feasibility pilot study for patients with PSC. Since there is no clear data in humans to guide in the dosing of ATRA in cholestatic liver disease, this initial pilot used the FDA-approved daily oral dose of 45 mg/mg^2 (2). The efficacy of ATRA and UDCA combination therapy is shown below regarding changes in alkaline phosphatase, AST, ALT, and reduction of bile acid intermediate C4.

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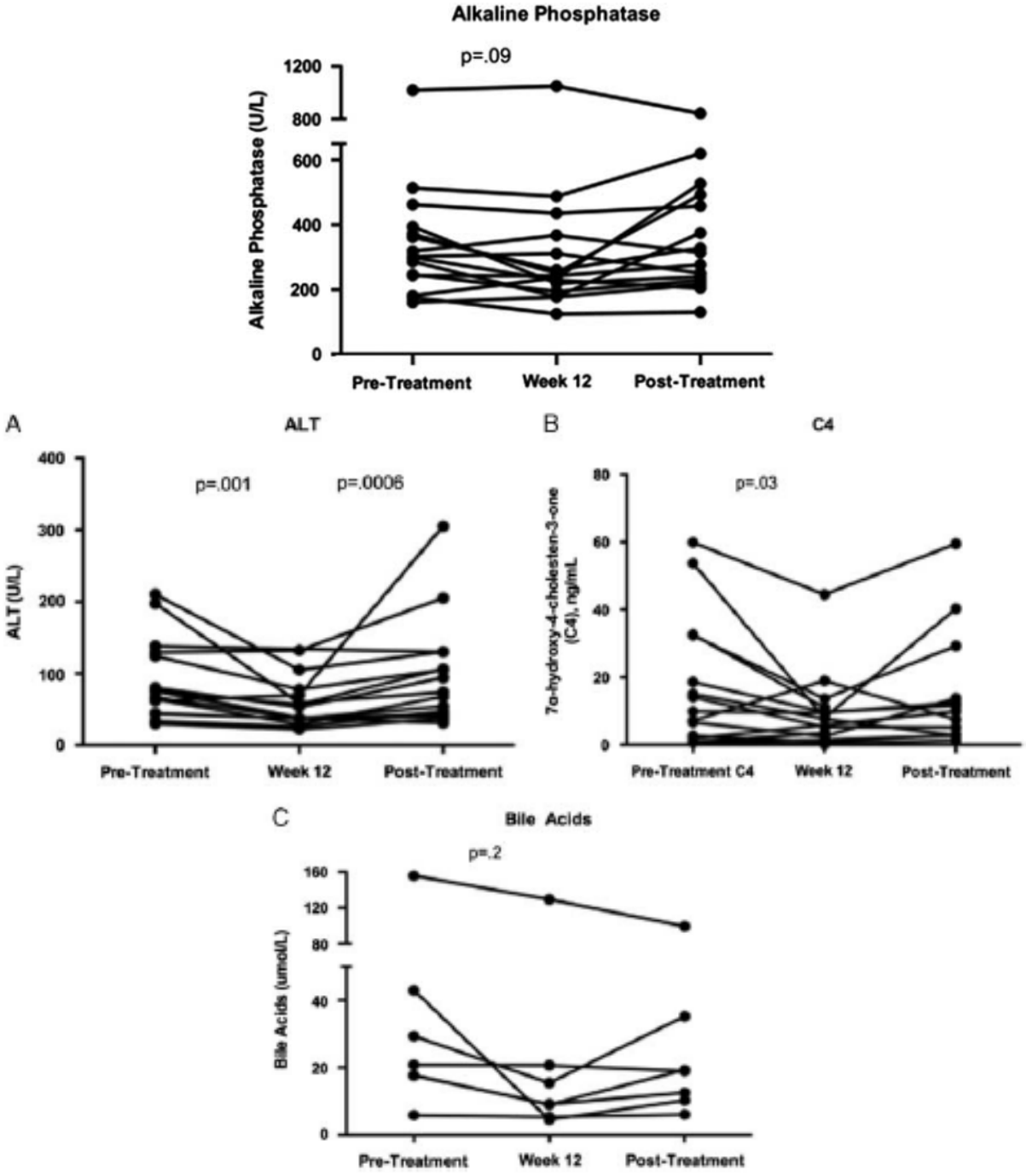

The recorded adverse effect frequencies in the combination study pilot are shown below.

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TABLE 2. Reported Adverse Effects

Adverse Effects	Frequency (%)
Headache	63
Tinnitus	26
Diarrhea	16
Dry skin/mucus membranes	10
Myalgia	5
Anemia	5

c. Marketing Experience

Oral ATRA has been FDA approved for human use in acute promyelocytic leukemia since 1995. It has been in clinical use for this condition since the early 1990s. It was marketed as Vesanoid by Roche Pharmaceuticals in 10 mg capsules. It is presently off patent and marketed as a generic drug as Tretinoin, 10 mg capsules.

3. Guidelines for the Investigator

The oral formulation of ATRA used in this study will not mirror what is used in clinical practice (generic Tretinoin) for patients with APL. Specifically, we will use a fixed dose of 10 mg twice daily of ATRA for all participating subjects, instead of the FDA-approved dose for ALP, of 45 mg/m^2/day. Comprehensive assessment of adverse events (AE) will be performed at each in-person study visit (baseline, week 4, week 12, week 24 and week 28) and also by phone on weeks 8 and 16.

Investigators using this product should be aware of potential adverse effects as described above, and if present should adhere to study protocol regarding notification of patients and review committees.

4. References

1. He H, et al. Combination of retinoic acid and ursodeoxycholic acid attenuates liver injury in bile duct-ligated rats and human hepatic cells. Hepatology 2011;53(2):548-57.
2. Assis, DN et al. Combination Therapy of All-Trans Retinoic Acid With Ursodeoxycholic Acid in Patients With Primary Sclerosing Cholangitis: A Human Pilot Study. J Clin Gastroenterol. 2017 Feb;51(2):e11-e16.
3. Product Information: VESANOID(R) oral capsules, tretinoin oral capsules. Roche Pharmaceuticals, Nutley, NJ, 2004.
4. Tallman MS, et al. All-trans-retinoic acid in acute promyelocytic leukemia. N Engl J Med. 1997;337:1021-8.
5. Bocher WO, et al. All-trans retinoic acid for treatment of chronic hepatitis C. Liver Int. 2008;28:347-54.
6. Allen JG, Bloxham DP. The pharmacology and pharmacokinetics of the retinoids. Pharmac Ther. 1989;40:1-27.

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7. Breccia M, et al. Clinical and biological features of acute promyelocytic leukemia patients developing retinoic acid syndrome during induction treatment with all-trans retinoic acid and idarubicin. Haematologica. 2008;93:1918-20.
8. Windhorst DB, Nigra T. General clinical toxicology of oral retinoids. J Am Acad Dermatol 1982; 6:675-682.
9. Shibata K, et al. Life-threatening hepatic toxicity caused by all-trans-retinoic acid in a patient with acute promyelocytic leukaemia. Clin Lab Haemat 1994; 16:191-195.

2. Source: Identify the source of the drug or biologic to be used.
Oral ATRA has been FDA approved for human use in acute promyelocytic leukemia since 1995. It has been in clinical use for this condition since the early 1990s. It was marketed as Vesanoid by Roche Pharmaceuticals in 10 mg capsules. It is presently off patent and marketed as a generic drug as Tretinoin, 10 mg capsules.

a) Is the drug provided free of charge to subjects? ☒YES ☐NO
If yes, by whom?
Yale Liver Center Donor funds will be used to purchase the drug and provided to patients free of charge.

2. Storage, Preparation and Use: Describe the method of storage, preparation, stability information, and for parenteral products, method of sterilization and method of testing sterility and pyrogenicity.
Drug will be purchased from the manufacture. Storage of medication prior to distribution will take place at the Yale-New Haven Hospital Investigational Drug Service facilities.

Check applicable Investigational Drug Service utilized:

☒ YNHH IDS ☐ CMHC Pharmacy ☐ West Haven VA
☐ PET Center ☐ None
☐ Other:

Note: If the YNHH IDS (or comparable service at CMHC or WHVA) will not be utilized, explain in detail how the PI will oversee these aspects of drug accountability, storage, and preparation.

3. Use of Placebo: ☒Not applicable to this research project

If use of a placebo is planned, provide a justification which addresses the following:

a) Describe the safety and efficacy of other available therapies. If there are no other available therapies, state this. *Write here*

b) State the maximum total length of time a participant may receive placebo while on the study. *Write here*
c) Address the greatest potential harm that may come to a participant as a result of receiving placebo. *Write here*
d) Describe the procedures that are in place to safeguard participants receiving placebo.

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Write here

4. Continuation of Drug Therapy After Study Closure ☐Not applicable to this project
Are subjects provided the opportunity to continue to receive the study drug(s) after the study has ended?

☐ Yes If yes, describe the conditions under which continued access to study drug(s) may apply as well as conditions for termination of such access. *Write here*

☒ NO If no, explain why this is acceptable.
ATRA will be given for 24 weeks only.

B. DEVICES ☒N/A

1. Are there any investigational devices used or investigational procedures performed at Yale-New Haven Hospital (YNHH) (e.g., in the YNHH Operating Room or YNHH Heart and Vascular Center)?
☐Yes ☐No

If Yes, please be aware of the following requirements:

A YNHH New Product/Trial Request Form must be completed via EPIC: Pull down the Tools tab in the EPIC Banner, Click on Lawson, Click on "Add new" under the New Technology Request Summary and fill out the forms requested including the "Initial Request Form," "Clinical Evidence Summary", and attach any other pertinent documents. Then select "save and submit" to submit your request; AND

Your request must be reviewed and approved in writing by the appropriate YNHH committee before patients/subjects may be scheduled to receive the investigational device or investigational procedure.

2. Background Information: Provide a description of previous human use, known risks, and any other factors that might influence risks. If this is the first time this device is being used in humans, include relevant data on animal models.
Write here
3. Source:
   a) Identify the source of the device to be used. *Write here*
   b) Is the device provided free of charge to subjects? ☐Yes ☐No

4. Investigational device accountability: State how the PI, or named designee, ensures that an investigational device is used only in accordance with the research protocol approved by the HIC, and maintains control of the investigational device as follows:

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a) Maintains appropriate records, including receipt of shipment, inventory at the site, dispensation or use by each participant, and final disposition and/or the return of the investigational device (or other disposal if applicable): *Write here*

b) Documents pertinent information assigned to the investigational device (e.g., date, quantity, batch or serial number, expiration date if applicable, and unique code number): *Write here*

c) Stores the investigational device according to the manufacturer's recommendations with respect to temperature, humidity, lighting, and other environmental considerations: *Write here*

d) Ensures that the device is stored in a secure area with limited access in accordance with applicable regulatory requirements: *Write here*

e) Distributes the investigational device to subjects enrolled in the IRB-approved protocol: *Write here*

SECTION III: RECRUITMENT/CONSENT AND ASSENT PROCEDURES

1. Targeted Enrollment: Give the number of subjects:
   a. Targeted for enrollment at Yale for this protocol:
   Goal is 20 adult subjects with PSC.
   b. If this is a multi-site study, give the total number of subjects targeted across all sites: NA

2. Indicate recruitment methods below. Attach copies of any recruitment materials that will be used.

☐ Flyers	☒ Internet/web postings	☐ Radio
☒ Posters	☐ Mass email solicitation	☒ Telephone
☒ Letter	☒ Departmental/Center website	☐ Television
☒ Medical record review*	☒ Departmental/Center research boards	☐ Newspaper
☐ Departmental/Center newsletters	☒ Web-based clinical trial registries	☒ Clinicaltrails.gov
☒ YCCI Recruitment database	☒ Social Media (Twitter/Facebook):	

☒ Other: 1. Subjects may be referred or may self-refer from web 2.The use of the Liver Registry database HIC 0603001208REG. (in the consent form of the registry it asks if the patient "I agree to allow other Liver Center investigators to contact me directly to participate in specific research studies. Yes____ No____"

* Requests for medical records should be made through JDAT as described at http://medicine.yale.edu/ycci/oncore/availableservices/datarequests/datarequests.aspx

3. Recruitment Procedures:

a. Describe how potential subjects will be identified.

Recruitment Procedures:
Describe how potential subjects will be identified.

Potential subjects will be identified from patients in the investigators' caseloads and may also be referred verbally, informally or formally by other physicians at Yale or community, to

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contact or be contacted by one of the investigators. As the trial will be listed on clinicaltrials.gov, yalestudies.org and the YCCI clinical trials website there is a possibility that potential patients may contact the research staff after seeing the trial listing on the website.

We will use YCCI resources to assist in subject recruitment. These resources include the YCCI recruitment center, the YCCI website, social media and Help Us Discover database to identify and notify patients.

The study team will also use the JDAT list medical record review for prescreening and recruitment. First the team will verify the patient is part of one of the investigators' caseloads. If they are part of one of the investigators caseload, then the patient will be contacted in a way that the investigator deems most appropriate for that patient, based on their 'patient - treating physician' relationship. Contact may be made by the treating physician, covering physician, trial coordinator and/or others approved to work on the trial. Contact can include (but not limited to) discussing the trial in person and/or giving the patient a flyer / letter at the patients upcoming clinic visit, calling the patient to ask if they would be interested in hearing about the study, sending the patient a my chart message, sending the patient an email with a letter / flyer. The only case in which we would not contact the patient who is part of an investigators caseload is if that patient initialed "No" to "I agree to allow other Liver Center investigators to contact me directly to participate in specific research studies. Yes____ No____" on the consent form for HIC # 0603001208 titled "Yale Liver Center Patient Registry and Serum/Tissue Bank."

If the identified patient is not part of the physicians' caseloads then the study team (treating physician, covering physician, trial coordinator and/or others approved to work on the trial) will contact the patient's current provider (via phone, an EPIC in basket, letter or in person meeting) this contact method will be based on the investigators' discretion and any 'provider – provider' relationship. During this contact, the study team member will provide all necessary information for the patient's current provider to determine the best way to approach the patient about the study. Necessary information may include inclusion exclusion criteria, study duration, study intervention, study goals, etc. The current provider may want to approach and/or have a study team member approach their patient about the trial via the patients next clinic visit, phone call, my chart message, email or mail and they may either discuss the trial with the patient directly, giving the patient a flyer / letter and/or asking the patient if a member of the study team may contact them directly. The study team will heed the current provider's suggested approach method.

The study team will also use the JDAT my chart and letter mailing feature, for all the patients who cannot be reached via one of the above methods. The study team would use JDAT to anonymously send the patient a my chart message or mailed letter. In this way we would not have any information about the patients, or which patients were contacted, and would only be able to get information if they contacted us about the study.

b. Describe how potential subjects are contacted.

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The principal investigators, sub-investigators and/or delegates under their direct supervision will contact their own patients or potential subjects will contact one of the investigators.

c. Who is recruiting potential subjects?
The principal investigators, sub-investigators and/or delegates under their direct supervision.

4. Assessment of Current Health Provider Relationship for HIPAA Consideration:
Does the Investigator or any member of the research team have a direct existing clinical relationship with any potential subject?

☐Yes, all subjects

☒Yes, some of the subjects

☐No

If yes, describe the nature of this relationship.
The investigators may have a health care provider relationship with potential subjects.

5. Request for waiver of HIPAA authorization: (When requesting a waiver of HIPAA Authorization for either the entire study, or for recruitment purposes only. Note: if you are collecting PHI as part of a phone or email screen, you must request a HIPAA waiver for recruitment purposes.)
Choose one:

☐ For entire study

☒ For recruitment/screening purposes only

☒ For inclusion of non-English speaking subject if short form is being used and there is no translated HIPAA research authorization form available on the University's HIPAA website at hipaa.yale.edu.

i. Describe why it would be impracticable to obtain the subject's authorization for use/disclosure of this data:
It is impracticable to obtain authorization from potential participants who call after seeing the trial posted on the web. Potential participants will volunteer information about their health and ask specific information via telephone prior to deciding whether or not they wish to provide the study team with their contact information or come into the Yale Liver Clinic to learn more about the trial, which is necessary prior to their signing the compound authorization form.

The study team will inform potential subjects, who call inquiring about the trial, that their contact information will be held by the research team until the individual comes into the clinic. Alternatively, any information that is collected during the course of the screening/inquiry call will be destroyed should the individual choose not to follow up with his/her call.

ii. If requesting a waiver of signed authorization, describe why it would be impracticable to obtain the subject's signed authorization for use/disclosure of this data:

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It is impracticable to obtain authorization from potential participants who call after seeing the trial posted on the web. Potential participants will volunteer information about their health and ask specific information via telephone prior to deciding whether or not they wish to provide the study team with their contact information or come into the Yale Liver Clinic to learn more about the trial, which is necessary prior to their signing the compound authorization form.

The investigator assures that the protected health information for which a Waiver of Authorization has been requested will not be reused or disclosed to any person or entity other than those listed in this application, except as required by law, for authorized oversight of this research study, or as specifically approved for use in another study by an IRB.

Researchers are reminded that unauthorized disclosures of PHI to individuals outside of the Yale HIPAA-Covered entity must be accounted for in the "accounting for disclosures log", by subject name, purpose, date, recipients, and a description of information provided. Logs are to be forwarded to the Deputy HIPAA Privacy Officer.

6. Process of Consent/Assent: Describe the setting and conditions under which consent/assent will be obtained, including parental permission or surrogate permission and the steps taken to ensure subjects' independent decision-making.
Consenting will take place at the Yale Liver Clinic, by speaking with the subjects in person at the time of the office visit with their provider.

The informed consent process will be conducted by IRB-approved consenting study personnel (including investigators, clinical research managers and clinical research coordinators) who have been delegated to conduct the informed consent process by the principal investigators. The Informed Consent process will consist of discussions between the investigator, consenting study personnel and potential subjects. Once a potential study participant is identified, an IRB-approved consenting personnel, knowledgeable about the clinical investigation and capable of answering questions raised by the potential study participant will conduct a consent interview. All potential subjects will be given a copy of the compound authorization and consent form to review at his/her leisure. Further, subjects will be encouraged to ask questions of the investigator and consenting study personnel regarding the protocol. All questions will be answered to the satisfaction of the subject. The investigator and consenting study personnel will explain the purpose and nature of the research study, the procedures that will be performed, the risks of the study drug and procedures, possible benefits, possible alternative treatments, the subject's rights and obligations as a participant, including the right not to participate in the study, without penalty and other information about the research study. During the consent process, should consenting study personnel be asked questions that are outside of their scope of practice, the subject will be referred to the investigator to ensure the question is answered to the satisfaction of the subject.

Subjects will be informed of any significant new findings that develop during the course of their participation in this study which may affect their willingness to continue to participate. The re-consent process will be conducted by IRB-approved consenting study personnel who have been

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delegated to conduct the informed consent process by the principal investigators. The new information will be clearly presented to the subject by the investigator and consenting study personnel. Subjects will be encouraged to ask questions and all questions will be answered to the satisfaction of the subjects. Should any significant new findings require prompt verbal notification to the subjects, the subjects will be verbally notified of the new information and the discussion will be documented in the electronic medical record system. Once the revised consent document is approved by the HIC, the subject will be formally re-consented by the investigator and IRB-approved consenting study personnel.

The consent document is signed and dated by the study participant, the investigator and other IRB-approved study personnel who participate in the informed consent process.

The investigator and other IRB-approved study personnel who participate in the informed consent process will document the informed consent process with potential subjects in the Electronic Medical Record (EMR) system.

7. Evaluation of Subject(s) Capacity to Provide Informed Consent/Assent: Indicate how the personnel obtaining consent will assess the potential subject's ability and capacity to consent to the research being proposed.
   If there is a history that a subject was declared to lack capacity to make medical decisions, or if the investigator or research manager determine during screening process that the potential subject does not have capacity to fully understand and assess the research project, that subject will not be offered participation in the pilot.

8. Non-English Speaking Subjects: Explain provisions in place to ensure comprehension for research involving non-English speaking subjects. If enrollment of these subjects is anticipated, translated copies of all consent materials must be submitted for approval prior to use.
   In cases where the subject does not understand English, the consent process can proceed with the following two options:

   A. The HIC "short consent" will be provided translated into a language the subject understands. The consent process will be mediated by a translator who speaks a language the subject understands, who can relay questions, answers, and information between the relevant parties. (Investigator, research manager, subject, etc.)

   B. A translation of the full consent will be provided translated into a language the subject understands. The consent process will be mediated by a translator who speaks a language the subject understands, who can relay questions, answers, and information between the relevant parties. (Investigator, research nurse, subject, etc.)

As a limited alternative to the above requirement, will you use the short form* for consenting process if you unexpectedly encounter a non-English speaking individual interested in study participation and the translation of the long form is not possible prior to intended enrollment? YES ☒ NO ☐

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Note* If more than 2 study participants are enrolled using a short form translated into the same language, then the full consent form should be translated into that language for use the next time a subject speaking that language is to be enrolled.

Several translated short form templates are available on the HRPP website (yale.edu/hrpp) and translated HIPAA Research Authorization Forms are available on the HIPAA website (hipaa.yale.edu). If the translation of the short form is not available on our website, then the translated short form needs to be submitted to the IRB office for approval via modification prior to enrolling the subject. *Please review the guidance and presentation on use of the short form available on the HRPP website.*

If using a short form without a translated HIPAA Research Authorization Form, please request a HIPAA waiver in the section above.

9. Consent Waiver: In certain circumstances, the HIC may grant a waiver of signed consent, or a full waiver of consent, depending on the study. If you will request either a waiver of consent, or a waiver of signed consent for this study, complete the appropriate section below.

☐Not Requesting any consent waivers

☒Requesting a waiver of signed consent:

☒ Recruitment/Screening only *(if for recruitment, the questions in the box below will apply to recruitment activities only)*

☐ Entire Study (Note that an information sheet may be required.)

For a waiver of signed consent, address the following:

- Would the signed consent form be the only record linking the subject and the research? YES ☒ NO ☐
- Does a breach of confidentiality constitute the principal risk to subjects? YES ☒ NO ☐

OR

- Does the research pose greater than minimal risk? YES ☐ NO☒
- Does the research include any activities that would require signed consent in a non-research context? YES ☐ NO ☒

☐ Requesting a waiver of consent:

☒ Recruitment/Screening only *(if for recruitment, the questions in the box below will apply to recruitment activities only)*

☐ Entire Study

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For a full waiver of consent, please address all of the following: NA

- Does the research pose greater than minimal risk to subjects?
  ☐ Yes *If you answered yes, stop. A waiver cannot be granted.*
  ☐ No
- Will the waiver adversely affect subjects' rights and welfare? YES ☐ NO☐
- Why would the research be impracticable to conduct without the waiver? *Write here*
- Where appropriate, how will pertinent information be returned to, or shared with subjects at a later date? *Write here*

SECTION IV: PROTECTION OF RESEARCH SUBJECTS

Confidentiality & Security of Data:

1. What protected health information (medical information along with the HIPAA identifiers) about subjects will be collected and used for the research?
   Subjects will be entered into the electronic Oncore system to track enrolment and eligibility. Protocol specific case report form (CRF) information which includes the subject's initials, age, date of birth & gender, no social security or names will be collected and used for research. Additional information provided on the CRFs would include patient treatment information as it specifically relates to the protocol i.e. patient visit information such as vitals, scan results, blood test results and other medical procedure results as required by the protocol.

2. How will the research data be collected, recorded and stored?
   The research data will be collected from medical records and recorded via the Oncore electronic database CRFs. Subjects name will not be recorded on these case report forms, instead a study number will be used. In addition, a copy of the subject's study record will be stored at the Yale liver center office space in The Anlyan Center (TAC). The TAC office space is locked and accessible to staff members of that office only.

3. How will the digital data be stored? ☐CD ☐DVD ☒Flash Drive ☐Portable Hard Drive ☒Secured Server ☒Laptop Computer ☐Desktop Computer ☐Other

4. What methods and procedures will be used to safeguard the confidentiality and security of the identifiable study data and the storage media indicated above during and after the subject's participation in the study?
   Passwords are required to access the medical records online; all paper files are stored in the TAC office space, which is locked. The Laptop is a Yale issued password protected ThinkPad, and the flash drives are Yale issued Iron Keys encrypted and password protected.

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All portable devices must contain encryption software, per University Policy 5100. If there is a technical reason a device cannot be encrypted please submit an exception request to the Information Security, Policy and Compliance Office by clicking on url http://its.yale.edu/egrc or email it.compliance@yale.edu

5. What will be done with the data when the research is completed? Are there plans to destroy the identifiable data? If yes, describe how, by whom and when identifiers will be destroyed. If no, describe how the data and/or identifiers will be secured.
   The results of the research may be published. Published reports will not include participant names or any other information that would identify them. All data is stored for the required amount by the FDA and then until the PI reports that the records may be destroyed. The records will either be stored in the locked office space in TAC or in a secure medical storage warehouse (Iron Mountain).

6. If appropriate, has a Certificate of Confidentiality been obtained? NA

SECTION V: POTENTIAL BENEFITS

1. Potential Benefits: Identify any benefits that may be reasonably expected to result from the research, either to the subject(s) or to society at large. (Payment of subjects is not considered a benefit in this context of the risk benefit assessment.)
   Potential clinical benefit may result to the subject if the low dose ATRA is efficacious for reducing effects of PSC, although subjects will clearly be told (and read in the consent form) that this research pilot study is exploratory and that the goal is to provide scientific information regarding drug efficacy, not to offer proven clinical benefits to individual subjects.

SECTION VI: RESEARCH ALTERNATIVES AND ECONOMIC CONSIDERATIONS

1. Alternatives: What other alternatives are available to the study subjects outside of the research?
   The alternative is non-participation. Non-participation in the study will have no impact on their present and future clinical care as patients at Yale Liver Clinic. Patient who do not wish to enroll as study subjects will continue to be treated by their hepatologists as per routine care.

2. Payments for Participation (Economic Considerations): Describe any payments that will be made to subjects, the amount and schedule of payments, and the conditions for receiving this compensation.
   The subject will not receive any monetary compensation for their participation in this study.

3. Costs for Participation (Economic Considerations): Clearly describe the subject's costs associated with participation in the research, and the interventions or procedures of the study that will be provided at no cost to subjects.
   The medication ATRA will be provided at no cost to the subjects. Blood work, office visits, all study procedures and parking will be paid for by the study and will not be charged to the subject.

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4. In Case of Injury: This section is required for any research involving more than minimal risk, and for minimal risk research that presents the potential for physical harm (e.g., research involving blood draws).

    a. Will medical treatment be available if research-related injury occurs? Yes
    b. Where and from whom may treatment be obtained? Any medical facility
    c. Are there any limits to the treatment being provided? No
    d. Who will pay for this treatment? The subject's Insurance Provider. If, as a result of participation in the study, the subject experiences injury from known or unknown risks of the research procedures as described, immediate medical care and treatment, including hospitalization, if necessary, will be available at the usual charge for such treatment. The subject or subject's insurance carrier will be expected to pay the costs of this treatment. No additional financial compensation for injury or lost wages is available.
    e. How will the medical treatment be accessed by subjects? Via contact, available at all times, with study investigators (hepatology physicians). The investigator would then coordinate any needed care

IMPORTANT REMINDERS

Will this study have a billable service? Yes ☒ No ☐

A billable service is defined as any service rendered to a study subject that, if he/she was not on a study, would normally generate a bill from either Yale-New Haven Hospital or Yale Medical Group to the patient or the patient's insurer. The service may or may not be performed by the research staff on your study, but may be provided by professionals within either Yale-New Haven Hospital or Yale Medical Group (examples include x-rays, MRIs, CT scans, specimens sent to central labs, or specimens sent to pathology). Notes: 1. There is no distinction made whether the service is paid for by the subject or their insurance (Standard of Care) or by the study's funding mechanism (Research Sponsored). 2. This generally includes new services or orders placed in EPIC for research subjects.

If answered, "yes", this study will need to be set up in OnCore, Yale's clinical research management system, for Epic to appropriately route research related charges. Please contact oncore.support@yale.edu

Are there any procedures involved in this protocol that will be performed at YNHH or one of its affiliated entities? Yes ☒ No ☐

If Yes, please answer questions a through c and note instructions below.
a. Does your YNHH privilege delineation currently include the specific procedure that you will perform? Yes ☒ No ☐
b. Will you be using any new equipment or equipment that you have not used in the past for this procedure? Yes ☐ No ☒

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c. Will a novel approach using existing equipment be applied? Yes ☐ No ☒

If you answered “no” to question 4a, or "yes" to question 4b or c, please contact the YNHH Department of Physician Services (688-2615) for prior approval before commencing with your research protocol.

IMPORTANT REMINDER ABOUT RESEARCH AT YNHH

Please note that if this protocol includes Yale-New Haven Hospital patients, including patients at the HRU, the Principal Investigator and any co-investigators who are physicians or mid-level practitioners (includes PAs, APRNs, psychologists and speech pathologists) who may have direct patient contact with patients on YNHH premises must have medical staff appointment and appropriate clinical privileges at YNHH. If you are uncertain whether the study personnel meet the criteria, please telephone the Physician Services Department at 203-688-2615. By submitting this protocol as a PI, you attest that you and any co-investigator who may have patient contact has a medical staff appointment and appropriate clinical privileges at YNHH.

APPROVED BY THE YALE UNIVERSITY IRB 10/3/2018 VALID THROUGH 9/19/2019