NOTICE OF OPPORTUNITY FOR CLINICAL TRIAL COLLABORATION

A --- Silymarin Product Development Program for use in NIH-Sponsored Clinical Trial for Liver Diseases

General Information

Document Type:	Special Notice
Solicitation Number:	Reference-Number-DK-05-0130
Posted Date:	March 4, 2005
Current Response Date:	May 23, 2005
Classification Code:	A -- Research & Development

Contracting Office Address

Department of Health and Human Services, National Institutes of Health, Nat'l Institute of Diabetes, Digestive, & Kidney Diseases, 2 Democracy Plaza, Suite 700W, 6707 Democracy Blvd., MSC 5455, Bethesda, MD, 20892-5455

DESCRIPTION: The National Center for Complementary and Alternative Medicine (NCCAM) and the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) of the National Institutes of Health (NIH) and of the Department of Health and Human Services (DHHS) seek collaboration with industry to participate in the Silymarin Product Development Program for use of silymarin, derived from the milk thistle plant Silybum marianum, in NIH-sponsored clinical trials for liver diseases.

INTRODUCTION:

The National Center for Complementary and Alternative Medicine (NCCAM), in collaboration with other components of the National Institutes of Health of the U.S Department of Health and Human Services, including the National Institute of Diabetes and Digestive and Kidney Diseases, is planning to form a Silymarin Product Development Program (PDP) and a Silymarin Research Network for Phase II clinical trials using silymarin, derived from the milk thistle plant Silybum marianum, for liver diseases. The initial stage of the Silymarin PDP presently is planned to consist of Phase I/II dose-ranging studies for silymarin in one or more of the following indications: chronic hepatitis C or non-alcoholic steatohepatitis. In addition, Phase I drug-drug interaction studies are planned. The total number of clinical trials to be performed in the initial stage of the PDP depends on the following factors: publication of a Request for Applications (RFA) for principal investigators to propose such studies; peer review of the applications by the NIH peer review system; and further evaluation and changes in the peer-accepted protocols by an NIH Silymarin Research Network Steering Committee. The second stage of the Silymarin PDP would consist of a Phase III pivotal trial of silymarin for one chosen clinical indication.

A decision point will occur after the initial stage of the Silymarin PDP. If the data from the Phase I /II trials suggest that proceeding to Phase III is appropriate, NCCAM, NIDDK and other NIH Institutes or Centers that may become involved, with the input of the selected Collaborator, are expected to plan a Phase III pivotal trial.

Therefore, NCCAM and NIDDK are seeking proposals in the form of capability statements from companies to enter into a collaboration to provide silymarin to support the Silymarin Product Development Program and the Silymarin Research Network. The selected Collaborator will be expected to enter into a Clinical Trial Agreement (CTA) with NCCAM. To facilitate the exchange of information regarding the PDP among the NIH components and the Collaborator, the selected Collaborator will also be expected to enter into an appropriate Confidential Disclosure Agreement preliminary to finalizing a CTA.

STUDY GOALS: The overall goal of the Silymarin Product Development Program is to evaluate a silymarin formulation for treatment or prevention or progression of hepatic disorders. It is unclear at this time if any or all of the disorders, chronic hepatitis C and non-alcoholic steatohepatitis, can be effectively aided by silymarin. Therefore, the initial stage of the silymarin PDP is to perform Phase I/II dose-ranging trials, and associated supportive Phase I studies, in whichever of these disorders can be reasonably studied. When the results of the initial stage of the Silymarin PDP are evaluated, a decision will be made by NCCAM, NIDDK and any other NIH Institutes or Centers that may be involved, with Collaborator's input, as to whether a Phase III pivotal trial for any indication is warranted.

SUPPLEMENTAL INFORMATION: The determination as to which disorders should be investigated will be made through the NIH process of publication of an RFA, reception of protocols in response to the RFA, peer-review of the proposed protocols, and further refinement of the protocols by the Silymarin Research Network Steering Committee. The Steering Committee will consist of the PIs of the several successful applications for the Silymarin Research network which may include up to 5 Clinical Centers and a single Data Coordinating Center. In addition, the Steering Committee will include NIH personnel, and may include the Collaborator as a non-voting member. The protocols contained in the successful applications for the Silymarin Research Network will be refined and finalized by the Steering Committee during the first year of the awarded Network. The protocols will then be implemented during years 2 and 3 of the Network.

The Clinical Trial Agreement (CTA) into which the selected Collaborator is expected to enter is an agreement designed to enable a collaboration between Government laboratories and industry. IT IS NOT A GRANT, AND IS NOT A CONTRACT FOR THE PROCUREMENT OF GOODS OR SERVICES. The NIH is prohibited from transferring funds to a CTA collaborator. Under a CTA, NIH can contribute facilities, staff, materials, and expertise to the effort. The Collaborator typically contributes materials and expertise to the collaboration. This will be an in-kind collaborative arrangement.

CAPABILITY STATEMENTS: A Selection Committee will utilize the information provided in the "Collaborator Capability Statements" received in response to this announcement to help in its selection of Industry Collaborator. It is the intention of the NCCAM and NIDDK that all qualified Collaborators have the opportunity to provide information to the Selection Committee through their capability statements. All Capability Statements will be reviewed by a scientific review panel.

The review panel will be considering its selection based upon data in the Capability Statement addressing the following criteria A-H. If no data is available, the potential Collaborator should so indicate.

A. CMC CRITERIA

In general, the details should be in conformity with FDA's expert advice with respect to acceptability for a pivotal trial. See for reference: "Botanical Drug Products " Guidance for Industry CDER, FDA, June 2004.

In particular:

1. Botanical raw material: Description, spectroscopic and/or chromatographic fingerprint, material processor, preparation of the raw material, quality control tests and analytical procedures, voucher specimen, certificate of analysis of the raw material, storage conditions.

2. Botanical drug substance: Description, chemical identification for active constituents and characteristic markers, specifications, manufacturing process, quality control tests, analytical procedures validation, reference standard, batch analysis, container, stability, container label.

3. Botanical drug product: Description, acceptance specifications, manufacturing process, quality control tests, validation reports of analytical procedures, batch analysis, container, stability.

4. Placebo

5. Labeling

6. Environmental assessment or claim of exclusion

B. NON-CLINICAL CRITERIA

1. Nonclinical data suggesting safety and efficacy of the product for treating chronic liver disease including hepatitis C and/or nonalcoholic steatohepatitis. Nonclinical data would normally include: efficacy in vitro and in animal models; toxicity after single and multiple doses in two species; reproductive toxicity in females and in males;

mutagenicity/genotoxicity in vitro and in vivo; carcinogenicity data if available; plasma levels of parent compounds and metabolites corresponding to acute and chronic toxicity. Because silymarin will be clinically administered for up to 1 year or more in the Phase II and eventual Phase III studies, chronic toxicity studies (with reversal) should be at least 3 months in duration and if possible 6 months in rodents and 9 months in non-rodents. Special pharmacology/toxicology studies, such as cardiovascular toxicity, neurological toxicity, and toxicity to indicated target organs, would be highly desirable.

2. Additionally, any available absorption, distribution, metabolism and excretion data should be submitted.

C. CLINICAL DATA

1. Clinical data suggesting safety and efficacy of the product for treating or preventing the progression of liver disease due to hepatitis (viral, alcoholic, or drug-induced) and/or steatosis.

2. Additionally, any available human absorption, distribution, metabolism and excretion data, in normal and in hepatic-compromised populations, should be submitted. Drug-drug interaction studies are highly desirable.

3. Instructions for use.

D. REGULATORY DATA

1. A copy of an Investigator Brochure for the product.

2. A list of the countries where your product(s) is in clinical testing or has been approved or marketed, if appropriate.

3. Whether there is an IND or Drug Master File (DMF) on file with the United States Food and Drug Administration (FDA). Please indicate when you filed the application and the current status of the IND or DMF. If you do not have an IND or DMF currently on file with the FDA, please indicate whether you will agree to submit sufficient and appropriate Chemistry, Manufacturing and Controls (CMC) documentation so that an IND can be filed by NCCAM.

E. ABILITY TO SUPPLY PRODUCT FOR PHASE I /II IND STUDIES

1. The manufacturer must be able to supply sufficient quantity of the formulated silymarin and matching placebo(s) within proposed specifications for the duration of the clinical trial. For this initial inquiry, manufacturers should assume that in Phase I/II trials, there will be a total of approximately 400-500 patients receiving silymarin daily for up to 6-to-12 months, and the daily dose will range from approximately 160 mg three times daily to approximately 640 mg three times daily.

2. Manufacturing capacity (batch size) for the product.

3. Please indicate when the appropriately packaged final formulation of silymarin could be made available to the NIH for use in clinical studies.

F.ABILITY TO SUPPLY PRODUCT FOR PHASE III PIVOTAL TRIALS

If Phase II and other supporting studies suggest to the NIH, with Collaborator's input, that a Phase III trial for a clinical indication is appropriate, ability to supply product for approximately 2000 patients administered silymarin, in dosages to be determined, but possibly 320-to-640 mg 3-times-a-day, for 2 years.

G. ABILITY TO PROVIDE OTHER SUPPORT FOR CLINICAL TRIALS

1. Pharmacokinetic support: assay of silymarin levels in plasma samples drawn from patients in Phase II studies.

2. Other clinical trial support

H. ALLOW FOR PROMPT PUBLICATION OF RESEARCH RESULTS

The statement must address willingness to allow for prompt publication of research results.

TERMS: The Collaborator will be expected to execute a Clinical Trial Agreement. An example of such CTA will be promptly provided to potential Collaborators upon written request to:

Peter T. DiMauro, Ph.D., Technology Development Specialist
NIDDK Office of Technology Transfer and Development
12 South Drive, MSC 5632
Bethesda, MD 20892-5632.

No funding from the government is available.

SUBMISSION DATES: A written statement of interest must be submitted by **May 9, 2005** and all Collaborator Capability Statements must be submitted by **May 23, 2005.**

Submit statements of interest and capability statements to:

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12 South Drive, MSC 5632
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Telephone: (301) 451-3636

Email: Rochelle.Blaustein@Nih.Gov
Fax: 301-402-7461.

For Scientific Inquiries contact:

Jonathan (Josh) Berman MD PhD FAAP
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http://TechDev.NIDDK.NIH.GOV/SilymarinPDP.pdf