HANDLE PBC RFP:

cHaracterizing and Addressing uNmet meDicaL nEeds in PBC

Primary biliary cholangitis (PBC) is a chronic, progressive autoimmune cholestatic liver disease. It is characterized by progressive destruction of bile ducts, leading to impaired liver function and a decline in patient quality of life[1,2]. The reported prevalence rates of PBC vary worldwide and are estimated to be between 1.91 to 40.2 cases per 100,000 individuals[3]. PBC disproportionally affects middle-aged women with a female-to-male ratio of approximately 10:1[4]. Despite currently available therapeutic interventions, PBC can progress to cirrhosis, necessitating liver transplantation in severe cases and potentially culminating in patient mortality[5].

The disease course of PBC may vary for each patient, with up to 40% of patients developing cirrhosis in 10 years[6]. Patients progressing to end-stage liver disease are at risk of its associated complications, including liver failure and hepatocellular carcinoma, which may result in premature death[7]. Patients with PBC may experience clinical symptoms including pruritus, fatigue, impairment of memory and concentration, and abdominal complaints, with a clear impact on the health-related quality of life[8-11]. Due to the frequently severe outcomes associated with PBC, there remains an important need to characterize the natural history and symptom burden associated with PBC.

To guide disease management, efforts have been made to develop and improve prognostic tools for PBC. Many large clinical trials use alkaline phosphatase <1.67x ULN, with at least 15% decrease and normal bilirubin, but the correlation of these biomarkers to clinical outcomes requires further investigation[12]. Other key measures that have been used include the GLOBE Score and the UK-PBC Risk Score, both of which are intended to predict mortality or liver transplant[13,]. Additionally, other non-invasive methods to assess disease severity and hepatic fibrosis are currently being considered, such as transient elastography or MRI; potentially reducing the need for invasive prognostic implements such as biopsy[14,15]. As these measures become more broadly adopted in the management of PBC, they must be continuously validated and improved upon.

Recent developments in PBC have introduced several new approaches to the clinical practice & management of the disease, including novel therapeutic agents[16]. A well-defined care cascade may be crucial in optimizing the diagnosis, management, and overall well-being of patients with PBC. Despite this, there is a general lack of data on the current PBC care cascade, thus paving the way for targeted research efforts to address these unmet needs.

To characterize and address the unmet medical needs in PBC, Gilead is launching the HANDLE PBC RFP. The program will support individual projects with research funding. Applications to the RFP program should include projects that can be completed within 18 months and demonstrate clear objectives, include defined timelines, offer a comprehensive operational plan, propose data that has relevance to the medical community and policymakers, and include plans for the data to be submitted to relevant congresses and journals. The program is open to applications from the US and European countries.

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HANDLE RFP Research Topics

Gilead will evaluate and support select programs based on the following research topics in PBC:

1. **Natural history & clinical outcomes**
    a. Elucidate the incidence, prevalence, and time-to-event for liver-related outcomes such as clinically significant portal hypertension, esophageal varices, progression to cirrhosis, decompensated cirrhosis, and liver transplant
    b. Characterize and assess the risk of extrahepatic manifestations associated with PBC, including cardiovascular disease, overlapping autoimmunity, and other comorbidities
2. **Care cascade**
    a. Illustrate the current care cascade from diagnosis to treatment and identify barriers to optimal disease management, including disparities in healthcare access and outcomes in diverse communities
    b. Describe the proportion & characteristics of patients eligible for first- and second-line treatment, those receiving treatment, those who stop treatment, and reasons for stopping treatment
    c. Identify clinical predictors for patient segments who could benefit from more aggressive initial treatment, such as combination therapy at initiation or more rapid addition of second-line therapy
3. **Noninvasive test validation**
    a. Evaluate the accuracy of noninvasive measures such as alkaline phosphatase, bilirubin, GLOBE score, UK-PBC score, transient elastography, MRI, or other methods as prognostic tools to predict disease progression, estimate the risk of liver-related events, and aid management/treatment
4. **Patient burden**
    a. Characterize qualitatively & quantitatively the symptom burden associated with PBC & treatments over time, such as pruritis & fatigue
    b. Characterize the natural history of pruritis in PBC & evaluate potential biomarkers predictive of improvement in pruritis

RFP Application Criteria

- Both investigator-sponsored research study proposals and collaborative research study proposals (developed in conjunction with Gilead) will be considered; sponsors for collaborative research studies must be able to comply with GxP regulations
- The sponsoring institution must be based in the US or Europe
- Proposed research endpoints should be generalizable across countries/regions
- Research proposals should include a comprehensive publication plan to present study results in scientific forums, and to publish results in peer reviewed journals
- The proposed budget should be appropriately proportional with the study's scope, with minimal infrastructural/equipment costs
    - The proposed budget should include overhead costs and applicable taxes; overhead costs should not exceed 30% of the total budget
- The proposed study design will not take longer than 18 months to complete

- There must be no more than one sponsor for contract negotiations and/or Institutional Review Board (IRB) review
- For proposals using seladelpar* in the intervention, seladelpar should have regulatory approval for PBC at the time of study initiation in the country the study will be conducted in as well as in the population the study will be on
- Funding for or contribution of study drugs will not be provided
- Additionally, as the study sponsor, the principal investigator will be responsible for compliance with all laws and regulations applicable to research sponsors, including satisfying local requirements and obtaining all necessary regulatory approvals before beginning the study

*As of March 2024, seladelpar is an investigational agent whose safety and efficacy have not been confirmed by any regulatory agency

Application Process

To apply for consideration for funding under the HANDLE PBC RFP Program, you will need to submit a Letter of Intent** (LOI) that is no longer than two pages, contains a concise overview of the proposed project and includes the total estimated budget. Applicants should submit the LOI application in the Gilead OPTICS portal.

Gilead will evaluate and rank all letters of intent (LOIs) received on a rolling basis until funds are exhausted. **It is recommended to submit earlier than later to ensure that funding is available for your proposal.**

- June 1st, 2024 at 00:00 AM GMT: Submission window opens
- September 1st, 2024 at 23:59 PM GMT: Submission window closes

Questions about the RFP or the application process can be submitted to your local Gilead Medical Science Liaison. A review of the LOIs will result in invitations for selected LOI applicants to submit a full application with a detailed budget.

Gilead's approval of awards will depend on the availability of funds and receipt of meritorious and complete proposals. Awards shall be granted solely on the merit of the research and alignment with the criteria of this program.

**LOIs are not binding documents on either party. The purpose of the LOI is a brief summary of the proposed study to enable Gilead to determine on a preliminary basis whether the proposed study and related budget are aligned with the criteria, timeline, and scope of this RFP.

No Guarantee of Funding

Gilead reserves the right to approve or decline any application at its sole discretion. Submission of an LOI or a full application does not guarantee funding.

The program provides awards for proposals completed in up to 18 months. Awards shall be for research purposes only; routine medical care or other costs associated with routine medical care will not be considered for funding.

No Inducement or Reward

Gilead approval of awards does not take into account the past, present, or future volume or value of any business or referrals between the parties. Awards are not being given, directly or indirectly, as an inducement or reward with respect to the past or potential future purchase, utilization, recommendation or formulary placement of any Gilead product. Furthermore, except for the use of the Gilead product in an approved award/research, the awardee is not required to purchase, order, recommend or prescribe to any patients any products manufactured by or available through Gilead.

About Gilead Sciences

Gilead Sciences, Inc. is a biopharmaceutical company that discovers, develops and commercializes innovative therapeutics in areas of unmet medical need. The company's mission is to advance the care of patients suffering from life-threatening diseases worldwide. Gilead has operations in more than 30 countries worldwide, with headquarters in Foster City, California.

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