HANDLE PBC 2025 Request for Proposals (RFP):

cHaracterizing and Addressing uNmet meDicaL nEeds in PBC

Primary biliary cholangitis (PBC) is a chronic, autoimmune cholestatic liver disease characterized by progressive destruction of bile ducts that can lead to cirrhosis, liver failure, and in severe cases, patient mortality[1,2]. PBC patients often suffer from debilitating symptoms, such as pruritus and fatigue, and an overall decline in quality of life[1,2]. Despite the availability of multiple therapeutic interventions, questions remain around optimal clinical practice for managing disease progression and symptoms.

To guide disease management, efforts have been made to develop and improve prognostic tools for PBC. ALP is a widely used biomarker in PBC with cutoffs of 1.5X or 1.67X the upper limit of normal (ULN) often used to assess prognosis and treatment response[1,3,4]. However, many patients fall below these thresholds but still have persistently elevated ALP (i.e. above the ULN)[5]. The natural history and symptom burden in this population of "incomplete" responders has not been fully elucidated. Some studies indicate that ALP normalization could further improve long-term outcomes for these patients[6,7]. However, further research is needed to determine which patients benefit most from ALP normalization and how the duration of time spent above or below the ULN influences those outcomes.

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[8,9]. As these measures become more broadly adopted in the management of PBC, they must be continuously validated and improved upon.

To address outstanding questions around incomplete response, fibrosis regression, and the symptomatic burden of PBC, Gilead is relaunching the HANDLE PBC RFP. Proposals submitted to the RFP should include studies with the following characteristics: clear objectives, data analysis plans with sufficiently robust sample sizes, defined timelines, a comprehensive operational plan, data that is relevant to the PBC community (including healthcare providers, patients, and caregivers), and plans for the data to be submitted to relevant congresses and journals. Proposed studies should be completed within 18 months of initiation. Proposals requiring a longer duration should include a clear and well-justified rationale. The program is open to applications globally.

RFP Research Topics

Gilead will evaluate and support select proposals based on the following research topics in PBC:
Note: Studies may address one or more of the following topics; addressing all is not required.

1. **Characterize the clinical and demographic profiles, disease progression, and symptom burden in patients with an incomplete biochemical response to treatment**, defined as alkaline phosphatase (ALP) levels above the upper limit of normal (ULN) but below 1.67× ULN.
2. **Identify patient- and treatment-related factors[§] that influence the clinical impact of ALP normalization**, including but not limited, to patient clinical characteristics or duration of time above/below normal.
3. **Assess the utility of established non-invasive fibrosis markers** (e.g., transient elastography, Enhanced Liver Fibrosis [ELF]) in monitoring disease progression and evaluating treatment response in patients with PBC.
4. **Examine the broader impact of PBC-associated pruritus on patients and caregivers**, including associated symptoms, quality of life, functional status, and socioeconomic outcomes.

[§]While studies may explore treatment-related factors, proposals involving direct head-to-head comparisons of treatment agents will not be considered.

Additional research objectives will be considered for select geographies, including PBC epidemiology, natural history, and the clinical care cascade. Please contact your local medical science liaison with questions about whether a study proposal could be within scope.

RFP Application Criteria

- Both investigator-sponsored research (ISR) study proposals and collaborative research study proposals (developed in conjunction with Gilead) will be considered (link to additional information on ISR vs collaborative studies)
- Proposed research endpoints should be based on sound scientific hypotheses and generalizable across countries/regions
- Research proposals should include a comprehensive publication plan to present study results at scientific forums and to publish results in peer reviewed journals
- The proposed budget should be appropriately proportional with the study's scope
    - The proposed budget should include overhead costs and applicable taxes; overhead costs should not exceed 30% of the total budget
- The proposed study design should be feasibly executed within a reasonable timeframe proportional to the study's follow-up duration
- There must be no more than one sponsor for contract negotiations
- 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 and ethical approvals before beginning the study

Application Process

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

How to Submit an LOI in G. OPTICS for the HANDLE PBC RFP

- Create an account or log into your account in G. OPTICS
- Select "Letter of Intent (LOI)"
- Select "Request for Proposal (RFP) Program"
- Select "HANDLE PBC 2025" from the list of active RFPs
- Read through the requirements page and save a copy for reference
- Complete the required fields
- Submit the LOI
- For additional guidance, please refer to the "Help Documents" on the G. OPTICS page

Gilead will evaluate and rank all letters of intent (LOIs) received on a rolling basis until funds are exhausted.

- Submission window opens July 17th, 2025, at 00:00 (US Pacific Time)
- Submission window closes September 18th, 2025 at 23:59 (US Pacific Time)

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 proposal with a detailed budget.

LOIs will be rigorously reviewed by Gilead's internal committee. Each complete LOI that meets program requirements will be assigned to multiple reviewers. Each reviewer will review the LOI and evaluate how well the proposal addresses the RFP, the potential impact of the study, the strength of the objectives/study design, sustainability/scalability of the proposal/intervention, and the site's and study team's ability to recruit the proposed study population and execute on study objectives. Investigators with the top submissions will be offered the opportunity to submit a full application including a detailed budget, adequate and proportional to the study's scope, which will be similarly reviewed.

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.

No Guarantee of Funding

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

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.

References

1. Lindor KD, et al. *Hepatology*. 2019;69(1):394-419 (Primary Biliary Cholangitis: 2018 Practice Guidance from the American Association for the Study of the Liver [AASLD])
2. American Liver Foundation. Primary biliary Colangitis (PBC). Updated March 22, 2024. Accessed January 6, 2023. https://liverfoundation.org/liver-diseases/autoimmune-liver-diseases/primary- biliary-cholangitis-pbc/
3. EASL. *J Hepatol.* 2017;67(1):145-172.
4. You H, et al. *Hepatol Int*. 2022 Feb;16(1):1-23
5. Lammers, et al. *Gastroenterology*. 2014;147:1338–1349
6. Perez, et al. *Am J Gastroenterol*. 2020 Jul;115(7):1066-1074.
7. Corpechot, et al. *Hepatology*. 2024 Jan 1;79(1):39-48.
8. Corpechot C, et al. *Gastroenterology*. 2014;146:970-979
9. Eaton JE, et al. *J Gastroenterol Hepatol.* 2016;31:1184-1190

Footnotes:

***LOIs are not binding documents for 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.*