CADTH REIMBURSEMENT REVIEW

Patient and Clinician Group Input

Elafibranor (TBC)

Ipsen Biopharmaceuticals Canada Inc.

Indication: Elafibranor is anticipated to be approved by Health Canada for the treatment of primary biliary cholangitis (PBC) in combination with ursodeoxycholic acid (UDCA) in adults with an inadequate response to UDCA, or as monotherapy in adults unable to tolerate UDCA.

December 13, 2024

This document compiles the input submitted by patient groups and clinician groups for the file under review. The information is used by CADTH in all phases of the review, including the appraisal of evidence and interpretation of the results. The input submitted for each review is also included in the briefing materials that are sent to expert committee members prior to committee meetings.

Disclaimer: The views expressed in this submission are those of the submitting organization or individual. As such, they are independent of CADTH and do not necessarily represent or reflect the views of CADTH. No endorsement by CADTH is intended or should be inferred.

By filing with CADTH, the submitting organization or individual agrees to the full disclosure of the information. CADTH does not edit the content of the submissions received.

CADTH does use reasonable care to prevent disclosure of personal information in posted material; however, it is ultimately the submitter's responsibility to ensure no identifying personal information or personal health information is included in the submission. The name of the submitting group and all conflicts of interest information from individuals who contributed to the content are included in the posted submission.

CADTH

ELAFIBRANOR Patient Input for CADTH Reimbursement Reviews

Name of Drug: [redacted] (Elafibranor)
Indication: Primary Biliary Cholangitis
Name of Patient Group: Canadian Liver Foundation
Author of Submission: Lucy You

1. About Your Patient Group

The Canadian Liver Foundation (CLF) is a leading organization dedicated to promoting liver health, increasing public awareness and understanding of liver disease, and providing support to individuals affected by liver disease.

The CLF was founded in 1969 out of the passion and concern of a group of business leaders and doctors who believed that liver disease needed a champion. Since then, the CLF has relentlessly driven advancements in research, treatment, and support. We remain the only non-government organization in Canada focused on liver health and the main source of non-profit funding for all forms of liver disease, investing nearly 40 million dollars to date.

The CLF reaches millions of Canadians through our public and professional education programs, patient support programs, and outreach efforts. We advocate for all Canadians affected by liver from newborns to seniors, including patients and their caregivers. Our organization can be found online at www.liver.ca.

2. Information Gathering

The CLF reached out to patients and caregivers who recently accessed our support services, including our National Help Line, email support services and in-person peer supports regarding primary biliary cholangitis. A total of 8 respondents provided input for this submission: 5 patients and 3 caregivers. A total of three patients were from Ontario and two from Alberta. One caregiver were from British Columbia and two from Ontario.

Additionally, insights from two healthcare professionals (HCPs) with expertise in liver disease management have been included. While their input was not collected specifically for this call for patient input, it offers valuable context on the management of PBC and considerations for the potential role of Elafibranor. This submission integrates these perspectives to provide a well-rounded view of the lived experience and clinical challenges associated with PBC.

3. Disease Experience

Primary biliary cholangitis (PBC) is a chronic, progressive autoimmune liver disease that primarily affects middle-aged women but can also occur in men and younger adults. PBC causes the immune system to attack the small bile ducts in the liver, leading to bile build-up, inflammation, and scarring. Over time, this can result in significant liver damage, cirrhosis, and eventually liver failure. Symptoms such as severe fatigue, itching (pruritus), and joint pain significantly impair quality of life, leaving patients unable to maintain normal daily activities. PBC also brings emotional and physical challenges, both for patients and their caregivers.

Currently, ursodeoxycholic acid (UDCA) is the first-line treatment for PBC. However, up to 40% of patients do not respond adequately to UDCA, leaving them at higher risk of disease progression and persistent symptoms. For these patients, new second-line therapies offer hope for improved disease management and quality of life.

The disease experience is felt by both those living with primary biliary cholangitis, as well as their caregivers and loved ones. Below are quotes from those affected by primary biliary cholangitis and their experience in managing the disease.

"Fatigue is the worst. I'd love a treatment that lets me feel like myself again."

"People think liver disease means I was a drinker, but I've never touched alcohol. It's exhausting to explain my condition over and over."

"If something could stop the itching, it would change my life completely."

"I see how hard my mom tries—taking her medication, following every guideline—and yet she's still struggling."

"Current treatments sometimes make me feel worse in other ways."
"My father's health shouldn't be left to decline without hope for improvement."

"We live far from a major city, and it's hard to access specialists or even regular follow-ups for my daugther."

"I want something that actually prevents damage, not just manages the symptoms."

"My partner is so tired all the time. I want to help more, but I don't always know what they need."

"*My ALP levels are still high. It feels like I'm just waiting for my liver to get worse."*

4. Experiences With Currently Available Treatments

The treatment for patients with primary biliary cholangitis (PBC) is often tailored to each individual's needs, with the goal of managing symptoms and slowing disease progression. The first-line treatment, ursodeoxycholic acid (UDCA), is commonly prescribed to improve bile flow, reduce liver enzyme levels, and manage symptoms such as fatigue and itching. For some patients, UDCA can lower alkaline phosphatase (ALP) levels and improve overall liver function. Antihistamines like hydroxyzine may be used to control itching, while skin moisturizers and lifestyle changes are often recommended to alleviate discomfort. For patients who do not respond adequately to UDCA, second-line therapies such as obeticholic acid (OCA) may be considered, though access and side effects can be limiting factors for some. Regular monitoring through blood tests and imaging remains essential to track disease progression.

Despite these available treatments, many patients continue to experience significant symptoms and insufficient disease control. In a recent survey conducted by the Canadian Liver Foundation, 30% of respondents reported that current medications, including UDCA, were not effective in managing their symptoms or preventing disease progression. These findings highlight the urgent need for alternative therapies that can address the unmet needs of patients with PBC.

Patients shared their experience with primary biliary cholangitis and their current treatment options. Below are quotes from these individuals with primary biliary cholangitis or their caregivers and loved ones on the impact current treatment has had on their disease.

"UDCA has helped lower my liver enzymes a bit, but it hasn't stopped the constant itching or the exhaustion. I'm still not able to do the things I used to."

"The biggest side effect for me is stomach upset. I have to take it with food to manage the nausea, but it's not always enough."

"UDCA has helped a bit with my liver enzymes, but it hasn't stopped the fatigue or itching. I still feel like I'm fighting this disease alone." – Patient

"We're constantly juggling appointments, blood work, and medication schedules. It's overwhelming for our entire family." – Caregiver

5. Improved Outcomes

Patients have shared what outcomes they would like to see from new therapies and the difference it would make to them or their loved ones.

"I just want to stop itching all the time. It's impossible to focus at work or sleep through the night when I'm constantly uncomfortable."

"Even if the treatment takes more effort, like an injection or more frequent blood tests, I'd gladly do it if it meant I could feel better."

" Something that tackles the root of her disease, not just the symptoms. If a new drug could do that, it would ease so much of our worry about her future."

6. Experience With Drug Under Review

Elafibranor (brand name: Iqirvo) is a potential second-line treatment for primary biliary cholangitis (PBC) in patients who have had an inadequate response to ursodeoxycholic acid (UDCA). At the time of this submission, patients who provided feedback had not started treatment with Elafibranor themselves. However, some had heard about it as a second-line option being discussed by their healthcare providers. Access to the drug under review is currently limited to clinical trials or special access programs, and none of the respondents indicated direct experience with these pathways.

Compared to UDCA, respondents expressed hope that Elafibranor could address persistent symptoms such as fatigue and itching, as well as help normalize ALP levels more effectively. While they could not share personal experiences with its benefits or disadvantages, patients and caregivers noted that new treatments like Elafibranor represent an opportunity to fill the gaps left by current therapies.

Patients have shared that UDCA remains the first-line therapy they are using, often with limited success in controlling symptoms or disease progression. They hope that a second-line therapy like Elafibranor would not only improve clinical markers but also reduce the day-to-day burden of living with PBC. Respondents emphasized the importance of a treatment that is easy to use, such as an oral medication, and one that minimizes side effects to avoid further impacting quality of life.

Key values highlighted by patients and caregivers include accessibility, affordability, and the ability to provide symptom relief while halting or slowing liver damage. While Elafibranor is not yet widely available, patients anticipate it being particularly helpful for those who have not responded adequately to UDCA, providing a much-needed alternative for this subgroup of PBC patients. The potential for fewer side effects and improved liver health outcomes could bring significant benefits to both patients and their caregivers, who often shoulder much of the emotional and logistical burden of managing this chronic condition.

7. Companion Diagnostic Test

The companion diagnostic testing is a blood test done to monitor the ALP liver enzyme, at 4 weeks after an individual begins taking a drug, to monitor ALP levels. The drug under review, Elafibranor, is designed to lower ALP levels, in some patients they are lowered to normal levels.

8. Anything Else?

Is there anything else specifically related to this drug review that CADTH reviewers or the expert committee should know?

The Canadian Liver Foundation believes that Canadians living with primary biliary cholangitis (PBC) deserve timely and equitable access to effective treatment options, regardless of geographical location, financial status, or disease severity. Addressing the full burden of PBC requires a comprehensive approach that goes beyond managing symptoms to include mental health, caregiver support, and holistic disease management.

PBC is a chronic, progressive condition that significantly disrupts the lives of those affected. Symptoms such as fatigue, itching, and joint pain often persist despite treatment, diminishing patients' ability to work, maintain relationships, and engage in daily activities. The uncertainty of disease progression frequently contributes to mental health challenges, including anxiety and depression, leaving patients feeling isolated and overwhelmed.

Caregivers also bear a heavy burden, often experiencing burnout, emotional exhaustion, and financial strain as they support their loved ones. Whether it involves managing appointments, navigating treatment plans, or providing emotional and physical care, the demands on caregivers are constant and impactful, affecting their own health and well-being.

Effective management of PBC must address these challenges holistically. This includes ensuring access to proven and emerging therapies that improve patient outcomes while minimizing side effects, as well as offering lifestyle interventions such as dietary guidance and exercise programs. Mental health support for patients and caregivers alike is critical, as is access to resources that ease the logistical and financial challenges of disease management.

The Canadian Liver Foundation underscores the importance of expanding therapeutic options and eliminating barriers to care. Provincial borders, financial inequities, or systemic challenges should never limit access to treatments or resources. By ensuring that patients across Canada can receive the best possible care, we can improve quality of life for those living with PBC and their families while reducing the overall burden of this disease.

Appendix: Patient Group Conflict of Interest Declaration

To maintain the objectivity and credibility of the CADTH reimbursement review process, all participants in the drug review processes must disclose any real, potential, or perceived conflicts of interest. This Patient Group Conflict of Interest Declaration is required for participation. Declarations made do not negate or preclude the use of the patient group input. CADTH may contact your group with further questions, as needed.

1. Did you receive help from outside your patient group to complete this submission? If yes, please detail the help and who provided it.

   No

2. Did you receive help from outside your patient group to collect or analyze data used in this submission? If yes, please detail the help and who provided it.

   No

3. List any companies or organizations that have provided your group with financial payment over the past 2 years AND who may have direct or indirect interest in the drug under review.

   The Canadian Liver Foundation (CLF) is committed to bringing liver research to life for all Canadians through liver research, education, patient support and advocacy. The CLF receives funding from a variety of sources with the majority coming from donations from individuals across the country. We use these funds to support CLF liver awareness, education, patient support and research grant programs.

   The CLF receives some program funding in the form of unrestricted educational grants from pharmaceutical companies. Grant agreements are established in support of activities initiated by the CLF and prohibit the funder from having any input or influence in program objectives or deliverables.

Table 1: Financial Disclosures

Check Appropriate Dollar Range With an X. Add additional rows if necessary.

Company	$0 to 5,000	$5,001 to 10,000	$10,001 to 50,000	In Excess of $50,000
N/A				

I hereby certify that I have the authority to disclose all relevant information with respect to any matter involving this patient group with a company, organization, or entity that may place this patient group in a real, potential, or perceived conflict of interest situation.

Name: Lucy You
Position: Vice President of Strategy, Health, and Technology
Patient Group: Canadian Liver Foundation
Date: December 10, 2024

CADTH

Name of Drug: Elafibranor
Indication: Primary Biliary Cholangitis
Name of Patient Group: Canadian PBC Society
Author of Submission: Gail Wright, PBC patient and President, Canadian PBC Society

1. About Your Patient Group

Founded in 2003, the Canadian PBC Society is a registered national charity dedicated to supporting Primary Biliary Cholangitis patients and their caregivers. Run by a strong team of volunteers, the Canadian PBC has grown to more than 1500 members. Our mission is to provide compassionate support, to develop and deliver information and education programs, to raise disease awareness, and to participate and sponsor research. Our website is:www.pbc-society.ca

2. Information Gathering

The information to complete this submission was gathered:

- **By electronic survey:** sent via email on August 25, 2024, and completed by 380 PBC patients.
- **In person**: during patient educational meetings held May – October 2024 and attended by more than 300 PBC patients and caregivers in Vancouver, Nanaimo, Calgary, Niagara Falls, Toronto, Ottawa, Moncton and Halifax.

3. Disease Experience

PBC, Primary Biliary Cholangitis is a chronic, progressive, rare, autoimmune liver disease. With no cure, current treatments aim to slow disease progression. Mainly diagnosed in women 35-60 years old, left untreated PBC will progress to cirrhosis and liver failure. PBC patients often experience complex health challenges. Patients' responsiveness to treatment is variable and those who have been "responsive" to treatment that slows disease progression, may become unresponsive over the course of their lives.

DISEASE BURDEN

Current treatments to slow disease progression do not treat symptoms and many PBC patients experience a heavy symptom burden. The interplay of symptoms in addition to the burden of one or more chronic comorbidities have a significant impact on mental health and quality of life. PBC patients often have several other autoimmune diseases and overlapping symptoms and may experience delayed diagnosis. When diagnosis is delayed, the disease progresses untreated and may accelerate the need for liver transplantation. When PBC is advanced, complications such as variceal bleeding, portal hypertension, hepatocellular carcinoma, and jaundice may be present.

Debilitating Fatigue - ***90% of survey respondents reported experiencing fatigue***

One of the most debilitating symptoms of PBC is fatigue. The fatigue, which is independent of the amount of sleep, has been described as "walking through custard" or "wearing a lead blanket" and renders simple daily tasks impossible.

"If my energy were a battery, it would never go above 20% charged."

"Everyday I wake up extremely tired. The energy level is so low that I'm losing my strength. I get scared I will end up in a wheelchair"

"It's exhausting and difficult to manage day to day. Especially with being young and having 2 young children, it's a level of exhaustion and short patience I didn't know existed. It feels like it rips the joy out of being a mother some days."

Unrelenting itch - ***52% of survey respondents reported experiencing PBC itch.***

The itch experienced by PBC sufferers goes far beyond the itch associated with a topical rash or insect bite. The itch is described as experiencing "a thousand ants crawling under the skin". The itch, often worse at night disrupts sleep further contributing to the debilitating fatigue. Continuous scratching does not relieve the itch but may be the cause of dangerous skin infections. The unrelenting itch and its effects have resulted in PBC patients requesting compassionate liver transplants related to feelings of suicide. PBC patient suicides have been reported. PBC itch that does not respond to medication is an indication for liver transplant.

"The itching causes sores all over my body, it can be embarrassing. I will no longer wear sleeveless tops because of it. I try really hard not to scratch too much in front of other people, as it too, can be embarrassing."

"The itching drives me crazy. I bruise very easily...my arms are always a mess with bruises and/or ripped skin that bleeds and scabs up"

"Before diagnosis, I was extremely itchy to the point of being suicidal. Nightmare, itching is horrid, sitting around with ice packs on your body is embarrassing and to shower is the same, get out of shower and severe itch is depressing."

Brain fog - ***72% of survey respondents reported experiencing "brain fog"***

"I guess the best way to describe it would be exhausting. The brain fog is tough to live with. Sometimes I feel like I have dementia. It's like being fogged in. I have to get people to repeat what they told me. Sometimes I forget right away. I don't like being in social situations as I find that exhausting. It can be quite depressing. Multi-tasking is out!"

Co-morbidities - ***81% of survey respondents reported living with one other chronic health condition***
52% of survey respondents reported living with more than one other chronic health condition

Along with PBC, patients often live with comorbidities like thyroid disease, osteoporosis, depression, anxiety, Sjogren's syndrome, Raynaud's syndrome, digestive disorder, fibromyalgia, and arthritis. It may be difficult to determine if symptoms are PBC related or a result of other comorbidities and therefore difficult to treat.

"Sometimes it is very hard, it is difficult to manage the fatigue, the fogginess and the anxiety. I try my best to cope but sometimes I feel that requires a lot of effort to build the mental capacity to deal with all the symptoms. "

"Continuously wonder if what I am feeling physically and mentally is related to PBC or is something else going on."

"Terrible...the fatigue and brain fog, joint pain is like nothing I can describe, and people just don't understand when you just can't function. At times I feel like a hypochondriac!! I can't imagine living like this forever!"

DISEASE IMPACT ON DAILY LIVING

Symptoms of PBC impact the ability to: work, carry out the tasks of daily living and maintain social relationships.

Inability to work - **29% of survey respondents aged 31-60 reported they were receiving disability benefits**

"Had to stop working due to fatigue, need to manage my daily activities based on fatigue, I feel like I am 10-15 years older compared to my friends regarding resistance, daily activities and social events."

"I had to take a disability leave from the job I loved as the pain, fatigue and brain fog was too much to keep working. After a long battle with disability plans, I am finally on CPPD and for financial reasons also made the decision to retire for extra income.

"The brain fog is awful some days and it makes working difficult."

Inability to carry out the tasks of daily living – **30% of respondents needed help with routine household tasks.**

"I have to manage chores and rest when needed. Driving any distance on my own- I don't do it."

"Constant fatigue means housework is done whenever my energy level permits."

"I have lost some independence as I now rely on my husband to drive me places when I am having a "bad brain day" because I get easily confused."

Inability to maintain social relationships- **34% of survey respondents reported cancelling plans due to PBC.**

"It is difficult to not be able to commit to events and make firm plans in case you are not feeling up to going when the time comes."

"I sometimes find it hard to carry on a conversation due to brain fog. Fatigue makes me not want to participate in physical activity and I do not attend activities that happen in the evening because I have no extra energy for an evening event. My friends do not invite me to a dinner where they won't be eating till 7 or later as I can't wait that long and need to leave."

"It's like living without knowing how you will feel tomorrow. It's losing friends who don't understand."

DISEASE IMPACT ON MENTAL HEALTH

Social isolation and depression

Social isolation and depression are two of the most common problems facing those living with PBC today. PBC fatigue may result in people feeling imprisoned within their home – frequently resulting in a loss of contact with friends, family, coworkers and community.

"It is lonely because nobody understands what I am going through. I feel labeled as lazy, or I am expected to push myself to exhaustion to keep up with a normal persons expectations (work, school, social). I sometimes feel stupid due to the brain fog, I cannot remember words or how to spell them - it can be overwhelming at times."

"Everything is unpredictable- how much energy I'll have daily, how much discomfort. It's psychologically stressful in addition to the physical stress. Basically, a recipe for depression and self flagellation. Cognitive and physical dissonance.

"I feel I survive I don't live. Extreme exhaustion and mental health make every day a struggle. I go from feeling like I'm wasting my life to what's my purpose in life this way."

Fear, stress and anxiety - ***20% of survey respondents reported suffering from anxiety***

Fear, stress and anxiety are common at various stages, and often heightened at diagnosis, or when treatments are ineffective, or when liver transplantation is presented as the only option.

"I rarely go out. I feel isolated and worry about the future and wish there was a way out of this. I worry every day about how I will manage which gives me anxiety. Everything is difficult and I would like to be able to participate in life again."

"Not knowing the future, when will I need a liver transplant, will I be too old to have the surgery "

"I have had periods of anxiety and worry due to PBC- wondering what impact it will have on my future health."

"PBC makes me uneasy because I am not sure of what is ahead as far as liver damage and symptoms. I am often hyper aware of changes in my body and worry I've reached the next phase of the disease. "

"It is always in the back of my mind. I now have cirrhosis, and I wonder how that will impact my life. I worry about getting cancer or another serious disease and not being able to handle the typical treatments because my platelets are low. All of this makes me feel anxious."

PBC patients need safe and effective treatment options that will stop disease progression and manage symptoms to prevent the suffering resulting from advanced liver disease and transplantation.

A Patient's 27-year journey with PBC to liver transplant

"The first thing and most important thing for me is as a single mother it greatly affected my ability to be 100% present for my daughter. Because of my fatigue and mental fog, I was almost like an absent parent. That is the biggest negative impact for me as a result of having PBC. I was only 43 when I was diagnosed then my daughter was 9 years old. I wasn't able to be the parent that I had always dreamed of being. Because of this she is now 36 years old, and we haven't spoken in 2 years, and I have a grandson that I haven't seen since he was 4 and he is now 6 years old. My liver disease stopped me from participating in so much and it ruined my chance to be a good 100% present mother. I didn't have a lot of family support in that area. PBC also affected my work life and social life. I had to miss many major events in my life because of PBC. I had to stop working earlier than what I had wanted to because of my PBC. I was on the waiting list for 5 years and went into a depression. I belonged to a support group of 10 people, and I was the last one to receive a liver transplant. Some of the members were on their 2nd liver while I was still waiting for mine. It was 14 years from the initial diagnosis until I got my transplant. A very long time which has impacted my quality of life severely. I am grateful that I received a transplant, and I am grateful to my doctors at the liver clinic pre-transplant and post transplant. I had to stop driving for 3 years just before my transplant because of brain fog. It has been a long road with many many ups and downs and your life is never the same."

A Patient's 15-year journey with PBC to liver transplant

"It was 15 years from first being diagnosed to transplant for my case, you gradually find ways to adapt to and accommodate the decline of your social and physical activities. You have a lot less mental strength, have difficulty coping with stress, have fatigue, digestive problems, brain fog, leg and other limbs cramping unpredictably which lead to not driving anymore and going for walk only with someone else present and the use of a cane for "just in case". Cramps were always on my mind. The overall joint and muscle pains were also part of the struggle and very limiting. The itch although manageable was enough to impede on a good night sleep. You have to manage the folds in the fabric on which you rest as it always seemed to be where the itch starts. You stop setting long term goals and are reluctant with starting any new projects. You get to the point when you feel useless and find no joy in life anymore. Once the ascites started, your life is completely taken over with medical appointments. You are cold and uncomfortable all the time and have no appetite. You are too sick to go anywhere. You become reclusive. Laughter is no longer part of your life. You essentially just exist."

4. Experiences With Currently Available Treatments

PBC patients need more treatment options - **25% of survey respondents reported that they did not feel their current treatment was improving their PBC**

Ursodeoxycholic (UDCA) was approved as a "first line" treatment for PBC patients in 1997.
UDCA has several possible sides effects including diarrhoea, nausea, dizziness, constipation, flu-like symptoms, stomach pain and hair loss; in addition, a small percentage of PBC patients are intolerant to UDCA.

UDCA has been effective in slowing the progression of the disease for approximately 60% of people with PBC. For the 40% of PBC patients with an inadequate response or intolerant to UDCA, the disease will progress to cirrhosis and eventually the need for transplantation (30-50%) or liver failure.

In 2017 obeticholic acid (OCA) was approved as a "second line" treatment for those with PBC who have an inadequate response to UDCA. Approximately 16% of survey respondents reported taking OCA and the majority (>60%) indicated it was helping to manage their disease. However, OCA has several possible side effects including increased "itch", rendering this treatment intolerable for some PBC patients. OCA is not indicated for those who have advanced liver disease with decompensated cirrhosis.

Neither UDCA nor OCA address PBC symptoms which carry a heavy burden, impacting quality of life and mental health.

5. Improved Outcomes

PBC patients hope to live both a long life and a life worth living. This means that there must be treatment options available throughout the course of this chronic, progressive disease to slow or halt disease progression and prevent the need for liver transplantation ***and*** manage symptoms. Each PBC patient has a unique experience and as the disease evolves over time, there is a need for a variety of treatment options, targeting a variety of treatment mechanisms to reduce the risk of disease progression.

25% of survey respondents reported they would like PBC treatments that addressed fatigue.
15% of survey respondents reported they would like PBC treatments that addressed itch.

"A cure would be wonderful. Also, treatments that stop deterioration."

"Offer these new treatments sooner so that disease does not progress"

"It's something that's always at the back of my mind. I worry about what happens if the treatment stops working for me. I'm getting older, if I were to require a liver transplant in the future would I be deemed to be too old? I worry about what the future may hold for me"

6. Experience With Drug Under Review

While we have no specific knowledge of patients who participated in the clinical trial for elafibranor, 7% of (August 25, 2024) survey respondents reported that they were currently participating in a clinical trial. Elafibranor was approved by the US FDA in June 2024 and PBC patients in the United States currently have access to this treatment option. Canadian PBC patients are requesting equitable access to elafibranor across Canada as soon as possible. It will provide a new second-line treatment option, targeting a different mechanism of action and that is not associated with increased itch, for Canadian PBC patients at risk of disease progression.

7. Companion Diagnostic Test

NA

8. Anything Else?

NA

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   No

2. Did you receive help from outside your patient group to collect or analyze data used in this submission? If yes, please detail the help and who provided it.

   Yes. Emily Johnson at the University of Alberta is a PhD candidate and first year medical student who assisted in the analysis of the survey data.

3. List any companies or organizations that have provided your group with financial payment over the past 2 years AND who may have direct or indirect interest in the drug under review.

Table 1: Financial Disclosures

Check Appropriate Dollar Range With an X. Add additional rows if necessary.

Company	$0 to 5,000	$5,001 to 10,000	$10,001 to 50,000	In Excess of $50,000
Advanz Pharma			X	
Calliditas Therapeutics			X	
Ipsen Biopharmaceuticals			X	
CymaBay Therapeutics			X	
Gilead Sciences			X	
Escient Pharmaceuticals			X	
GSK			X	
Intercept Pharmaceuticals			X	
Mirum Pharma			X	

I hereby certify that I have the authority to disclose all relevant information with respect to any matter involving this patient group with a company, organization, or entity that may place this patient group in a real, potential, or perceived conflict of interest situation.

Name: Gail Wright
Position: President
Patient Group: Canadian PBC Society
Date: December 6, 2024

CADTH

CADTH Reimbursement Review

Clinician Group Input

CADTH Project Number: SR0865-000
Generic Drug Name (Brand Name): Elafibranor ([redacted]
Indication: Primary Biliary Cholangitis
Name of Clinician Group: Canadian Network for Autoimmune Liver disease (CaNAL)
Author of Submission: Dr. Gideon Hirschfield, Director, Autoimmune Liver Disease Program, Francis Family Liver Clinic, UHN and Co-Principal Investigator CaNAL.

with

Dr. Andy Mason, Hepatologist, Professor of Medicine, University of Alberta.
Dr. Hin Hin Ko, Gastroenterologist, Clinical Associate Professor, University of British Columbia.
Dr. Julian Hercun, Hepatologist, Adjunct clinical professor, Université de Montréal.
Dr. Erin Kelly, Gastroenterologist, Assistant Professor, University of Ottawa.
Dr. Aliya Gulamhusein, Hepatologist, Toronto Centre for Liver Disease.
Dr. Mark G. Swain, Gastroenterologist, Professor of Medicine, University of Calgary.

1. About Your Clinician Group

The Canadian Network for Autoimmune Liver disease (CaNAL) is a pan-Canadian clinical research collaboration, with investigators spanning the country. We focus on primary biliary cholangitis, autoimmune hepatitis and overlap syndromes. Our website is www.canalregistry.ca . Our approach is to collect retrospective data across centres, as well as to consent patients where possible for prospective data collection, including symptoms.

Our outputs demonstrate well our interests, which focus on using clinical data from Canadian patients to learn about current care pathways, and identify unmet needs:

Loss of biochemical response at any time worsens outcomes in UDCA-treated patients with primary biliary cholangitis Roberts SB, Choi WJ, Worobetz L, Vincent C, Flemming JA, Cheung A, Qumosani K, Swain M, Grbic D, Ko HH, Peltekian KM, Abrahamyan L, Saini M, Tirona K, Aziz B, Lytvyak E, Invernizzi P, Ponsioen CY, Bruns T, Cazzagon N, Lindor K, Dalekos GN, Gatselis NK, Verhelst X, Floreani A, Corpechot C, Mayo MJ, Levy C, Londoño MC, Battezzati PM, Pares A, Nevens F, van der Meer A, Kowdley KV, Trivedi PJ, Lleo A, Thorburn D, Carbone M, Selzner N, Gulamhusein AF, Janssen H, Montano-Loza AJ, Mason AL, Hirschfield GM, Hansen BE; Canadian Network for Autoimmune Liver disease (CaNAL). JHEP Rep. 2024 Jul 8;6(10):101168.

Treatment response and clinical event-free survival in autoimmune hepatitis: A Canadian multicentre cohort study Plagiannakos CG, Hirschfield GM, Lytvyak E, Roberts SB, Ismail M, Gulamhusein AF, Selzner N, Qumosani KM, Worobetz L, Hercun J, Vincent C, Flemming JA, Swain MG, Cheung A, Chen T, Grbic D, Peltekain K, Mason AL, Montano-Loza AJ, Hansen BE; Canadian Network for Autoimmune Liver Disease (CaNAL). J Hepatol. 2024 Aug;81(2):227-237.

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The Canadian Association for the Study of the Liver (CASL) has endorsed this clinician input submission. CASL is a non-profit organization that seeks to eliminate liver disease through research, education and advocacy. Their members are experts on liver disease in Canada: hepatologists, gastroenterologists, pediatricians, surgeons, radiologists, researchers, nurses, trainees, community advocates, and patients and family partners.

https://hepatology.ca/about-casl/

2. Information Gathering

The CaNAL investigators are experienced Hepatologists with direct clinical and research experience in PBC. Information was gathered through personal experience in treating patients with PBC, literature review, participation as investigators in clinical trials, and virtual discussion among experts. The contributors to this submission are familiar with clinical trials in PBC including the ELATIVE Study, a phase 3 trial evaluating the efficacy and safety of elafibranor in patients with primary biliary cholangitis.

. 3. Current Treatments and Treatment Goals

PBC is managed by Gastroenterologists and Hepatologists in Canada. The top 5 broad facets to treatment are summarized below, and explained in the text that follows:

Criteria	Parameters
1. Diagnose PBC with confidence	**Elevated ALP and AMA are sufficient for the diagnosis of PBC, with biopsy being rarely needed** • Ultrasound excludes obstruction; MRCP can give false positive results • PBC is an inflammatory disease – ALT is regularly elevated and overlap with AIH is rare
2. Initiate first-line therapy with UDCA	**At diagnosis, UDCA at 13–15 mg/kg/day is recommended for all patients, and should be continued life-long** • Higher doses are not indicated
3. Manage symptoms in parallel to disease modifying therapy	**Symptoms particularly pruritus and fatigue, are an important part of living with PBC and should be carefully evaluated** • There are effective interventions for pruritus that patients should be offered • Patient support groups
4. Risk stratify your patients on UDCA	**Patients at greatest risk of disease progression should be prioritised for careful expert assessment** • PBC diagnosis at age < 50 years; • ALP > 1.5 xULN on UDCA • ALT > 2 xULN on UDCA • Abnormal bilirubin on UDCA • Advanced fibrosis
5. Use second-line therapy when indicated	**Second-line therapy should normally be considered for those patients with ALP > 1.5 xULN and/or abnormal conjugated bilirubin despite 12 months of UDCA therapy** • Obeticholic acid 5mg-10mg daily (licensed) • Re-purposed therapies and clinical trials (e.g. PPAR agonists)

Canadian practice sits between the US and Europe in delivery. Most patients are diagnosed in community GI practice, and most provinces have one or two hepatology programs that accept referrals for patients with more complex disease, those with pronounced symptoms, and those needing liver transplantation. At this time around 10000 people live with PBC in Canada; most estimates suggest incidence is around 3 per 100000 per year, and prevalence in women (who represent over 90% of patients) runs around 40 per 100000. Between 2000 and 2018 there were a total of 5722 primary liver transplantation procedures, of which 341 were for PBC. PBC is more common in Canadian First Nations, in whom treatment response is impaired and need for transplantation higher. The overarching goals of treatment in PBC focus on biochemical disease control, alongside alleviation of the symptom burden. As clinicians we hope to see our treatments make people live longer, feel better, and avoid the complications of end-stage liver disease (liver failure, bleeding, ascites, encephalopathy, hepatocellular carcinoma, and liver transplantation). Work from many investigators, including the CaNAL consortium, has contributed to the evidence base supporting the use of biochemical surrogates of disease control, focused on reaching normal alkaline phosphatase and bilirubin values if appropriate. Many investigators (individual centre studies as well as collaborative cohort studies) repeatedly demonstrate an association between outcome and ALP and bilirubin values during UDCA therapy. Further data from the GLOBAL PBC study group, to which significant Canadian data has been added, confirm that the best outcomes for people living with PBC treated with UDCA are in those with a normal bilirubin, and even once a patient has a normal bilirubin, there is better outcomes for those with a normal ALP. Therefore the diagnostic and treatment sequence in Canada approximates to:

1) Diagnose PBC usually based on readily available serum liver tests and autoantibodies, reserving liver biopsy for those with diagnostic uncertainty

2) At diagnosis appreciate a patients stage (by ultrasound and elastography if available), baseline risk for disease progression, and symptom burden

3) Prior to initiating therapy explain to the patient their disease, their risks, and their options, as well as signpost them to the Canadian PBC Society

4) Start Ursodeoxycholic acid in all patients (13-15mg/kg daily), explaining to patients this is usually a lifelong therapy, that over decades of research (interventional trials and real world data) has been shown to improve outcomes, but not symptoms

5) Address symptom burden where possible, including fatigue, sicca complex, pruritus, abdominal discomfort and arthralgias

6) Once on treatment (95% of patients tolerate UDCA well), explain to the patient that treatment efficacy is judged over time, usually after 6-12 months of therapy by biochemical control of disease, liver elastography over time, and ongoing symptom evaluation

7) Second line therapies are used in Canada in two settings- a) patients intolerant to UDCA and b) patients with insufficient biochemical control of disease. Outside of those intolerant to UDCA, the decision to start second line therapy on average occurs after 12 months of therapy, although with time and better disease awareness some are accelerating the decision to start second line therapy to 6 months after UDCA initiation. There are two approaches at this time, outside of trials. The first is the use of Obeticholic acid, which is an approved therapy in PBC. Patients for whom ALP remains >1.67xULN can be started on OCA, assuming they do not have significant pruritus, and do not have cirrhosis with portal hypertension (or decompensated disease). The alternative treatment paradigm at this time relies on off-label therapy with PPAR agonists. These are not approved agents for PBC, patients need counseling about their off label use, and pharmacies need instruction to waive the advice to not use in PBC that is present in the drug labels. Depending on province either Bezafibrate or Fenofibrate are prescribed. There is increasing evidence from trials and real world use that PPAR agonists can improve pruritus as well as control ALP values. In our experience community gastroenterologists are less willing to use off-label therapy.

8) Lifelong care continues to evaluate for disease progression to cirrhosis (usually by bloods, ultrasound and elastography) as well as manage symptoms. Aside from pruritus, options are few. For pruritus in Canada treatment usually focuses on i) anti-histamines [from family MDs pending consultation with a GI], cholestyramine/colestipol, bezafibrate, rifampin, gabapentin, naltrexone, and sertraline. Trials can be offered for patients with intractable pruritus, as well as plasmapheresis or transplantation.

9) Treatment targets are reviewed with the patient and assessed repeatedly over time and are accepted to focus on biochemical control of disease, prevention of late stage disease (using elastography as one surrogate) with an equal emphasis on quality of life improvements.

4. Treatment Gaps (unmet needs)

4.1. Considering the treatment goals in Section 3, please describe goals (needs) that are not being met by currently available treatments.

Unmet needs are substantial in PBC. Current therapies are limited in the following regards and Canadian Gastroenterologists and Hepatologists have been active participants in clinical trials that are targeting aspects of PBC care recognized to be in need of improvement:

UDCA- at least one-third of patients do not achieve sufficient biochemical control of disease and UDCA does not tackle symptoms;

Obeticholic acid- biochemical response as a second line agent is limited to around 48% of patients achieving a composite biochemical response; very few patients normalize ALP; OCA is associated with exacerbating pruritus; OCA cannot be used in patients with cirrhosis and portal hypertension; OCA elevates lipids;

Bezafibrate/Fenofibrate- since therapy is off-label access to care is restricted to providers with advanced Hepatology training. Hepatologists are under-represented in Canada; given the size of Canada, patients living with rare diseases can struggle to get timely diagnosis and care; notably in Canada First Nations have added health inequity when living with PBC, a disease more frequently encountered by this population, and with a greater chance of treatment failure to UDCA alone. More choice amongst licensed therapies will help equalize access to care. Bezafibrate/Fenofibrate can be associated with myalgias, elevated creatinine, and interaction with statins. There are also concerns about potential for liver toxicity with bezafibrate and fenofibrate;

Symptoms- there are no clearly defined therapies approved for symptom control in PBC. Therapies remain off label;

Care pathways – PBC is a rare disease and Canada is a very big country with varied health ; there are some provinces with higher rates of PBC, in part because of increased diagnosis and severity in First Nations;

Advanced cirrhosis with portal hypertension – As in most liver diseases there will remain patients who either present with late stage disease, or who progress on standard of care therapy to end-stage disease. In PBC this is a small but important part of clinical practice, and is a group of individuals with a need for new and emerging therapies.

5. Place in Therapy

5.1. How would the drug under review fit into the current treatment paradigm?

UDCA works through bile acid pool modification. Obeticholic acid works as a FXR agonist. Elafibranor, like other agents used globally, is a PPAR agonist. In the case of Elafibranor the PPAR specificity is alpha/delta (other new drugs target PPARs differently e.g. Seladelpar is a PPAR delta agonist recently approved by the FDA). At this time in Canada Elafibranor would be the first licenced PPAR agonist, alongside Bezafibrate

and Fenofibrate which are used off label. In the USA, Seladelpar, a PPAR delta agonist is approved for the treatment of PBC i.e. this class of agent is now emerging as a new part of approved PBC therapies generally. Obeticholic acid is a distinct therapy to the PPAR agonists, including in particular Elafibranor. Whilst both Obeticholic acid and Elafibranor target cholestasis, inflammation and fibrosis, Elafibranor does so through PPAR agonism, does not exacerbate pruritus, and in the studies to date can be used in patients with cirrhosis. Given experience of triple therapy (UDCA, OCA, Bezafibrate) published academically in non trial settings, it is fair to believe that in the treatment of PBC there is impact on disease through separate but complementary pathways i.e. the management of PBC cholestasis can be modulated by either FXR or PPAR agonists, and can be additive, but fundamentally it is good for patients to have choice of therapies.

Elafibranor would therefore be a second line agent, used like obeticholic acid. This would be based on one Phase 2 trial and one Phase 3 trial. It would be used alongside UDCA. With approval of Elafibranor clinicians will have a choice of Obeticholic acid and Elafibranor as licenced second line agents. Head to head comparisons have not been made between Obeticholic acid and Elafibranor. In the respective Phase 3 clinical trials the composite biochemical endpoint was met in 48% of patients receiving Obeticholic acid and 51% of those receiving Elafibranor. OCA caused pruritus, and there were elevations in lipids. Elafibranor did not exacerbate pruritus, and whilst not meeting a key pre-defined secondary endpoint of pruritus improvement, on secondary analyses pruritus did improve. Lipid values fell with Elafibranor. Elafibranor is therefore likely to be a second line agent that clinicians will consider instead of OCA. It will adjust current treatment away from off-label PPAR use, to labeled therapy, with improved safety monitoring as a result. Whether Elafibranor is better tolerated than off-label PPAR agonists such as Bezafibrate or Fenofibrate, will need to be evaluated in real-world use, but comfort for patients and prescribers will be heightened by use of an approved agent.

With access to Elafibrator, UDCA will remain first line therapy. Guidelines are unlikely to proscribe the sequence a clinician chooses which second line agent to use; they are more likely to address the available trial data, and align potential choices for clinicians to follow. That said, patients needing second line therapy who have pruritus will not be recommended to use OCA and patients with more advanced disease with portal hypertension will not be advised to use OCA. Patients with decompensated liver disease will not receive Elafibranor.

5.2. Which patients would be best suited for treatment with the drug under review? Which patients would be least suitable for treatment with the drug under review?

Care pathways in PBC have become quite clear and easy to follow. So long as a patient can receive a clear and confident diagnosis (which occurs in the majority without recourse to tertiary care), then initial therapy with UDCA can be initiated. Treatment goals should now be focused on achieving the best serum liver tests (normal ALP, normal bilirubin) alongside the best symptom control. This does not mean every patient needs to meet the same biochemical goals, and clinicians appreciate the need to individualise care to the patient, accounting for co-morbidities and liver disease stage. Elafibranor is likely to be used in a similar way to Obeticholic acid initially. This means we can expect that Elafibranor will be used predominantly as a second

line therapy in those patients with an ALP >1.67xULN. Patients intolerant to UDCA, will also be likely offered Elafibranor (just as they can be offered Obeticholic acid).

Diagnosis is relatively straight forward and tertiary programmes assist where doubt exists. No companion diagnostic tests are needed. Misdiagnosis should be rare. Therefore it is expected that the target population of patients living with PBC will be offered second line therapy in a safe manner.

Treatment response is primarily determined by following serum liver tests, In ELATIVE, the Phase 3 clinical trial, 51% of patients responded after 12 months of therapy (based on a composite biochemical response criteria). Based on the experience of Obeticholic acid, it is expected that real world use will match clinical trial data at the outset. It is not clear at this time how to define which patients will not achieve optimal biochemical or symptom control with Elafibranor. Based on existing experience it is expected that response will be less in those with the highest ALP at treatment initiation, those with most ductopenia, and those with most pruritus.

5.3 What outcomes are used to determine whether a patient is responding to treatment in clinical practice? How often should treatment response be assessed?

It is now accepted that biochemical response is a good marker of treatment efficacy, and emerging data from a consortium called the GLOBAL PBC study group, of which many Canadian sites contribute, have validated treatment response in second line therapies (Obeticholic acid, fibrates) as well as after UDCA alone. Therefore in the use of Elafibranor clinicians will look at serum liver tests predominantly. The outcomes used in clinical trials align with practice, with the caveat that clinicians will look predominantly at ALP values and their drop, as opposed to just dichotomous treatment responses used in trials for the purposes of drug registration. Clinicians are accustomed to the slow progression of PBC and whilst they seek long term data on survival, in the adoption of new therapies in PBC they are aligned clinically to use serum liver tests. Whilst clinicians recognize the importance of using therapies that attain the highest likelihood of ALP normalization, bilirubin normalization and improvement in symptoms, they also appreciate the evidence that supports ‘lower is better’ and the importance of tailoring therapy to individuals. Therefore at the least clinicians will hope to see an ALP <1.67 x ULN, but in patients with high risk disease they will accept an ALP drop of at least 20% as clinically valuable i.e. in those patients with very high ALP it is not likely any therapy will always drop the ALP to optimal levels but a meaningful fall is still impactful. In those patients with greatest need they will re-evaluate treatment choices and sequence of therapies based on how close the ALP can be to normal. Symptom response, in particular pruritus will be evaluated qualitatively in conjunction with the patient.

5.4 What factors should be considered when deciding to discontinue treatment with the drug under review?

In an evolving field of PBC therapies, and with expectation from clinicians that Canadian patients will have increasing choice over time, treatment sequencing and changes will focus on biochemical response, resolution of symptom, tolerability of drug and drug-drug interactions. Clinicians will take note of prescribing advice from regulatory agencies in order to use therapies safely. In the case of Elafibranor clinicians will carefully review and consider stopping therapy if serum liver tests deteriorate, if significant myalgias occur or

CK rises, and if creatinine rises. They will reconsider Elafibranor if there is concern about drug interactions, if a patient wants to conceive, or if the patient develops impaired liver function.

5.5 What settings are appropriate for treatment with [drug under review]? Is a specialist required to diagnose, treat, and monitor patients who might receive [drug under review]?

PBC is largely managed in ambulatory care by Gastroenterologists (Specialists). A smaller number of patients are seen by dedicated Hepatologists, who are also originally Gastroenterologists by training.

6. Additional Information

It is important to recognize the patient voice in treatment decisions in PBC care. The Canadian PBC Society has for a long time represented a strong support group for patients that clinicians turn to for patient education, and with which we and others have frequently collaborated with as regards addressing research, care and training. It would be fair to comment that the patients in Canada are engaged, recognize they live with a rare disease with unmet need, and are committed to ensuring Canadian patients have access to the therapies used to treat PBC around the world, and are mindful of the choices of drugs available to patients outside of Canada, as well as the contribution of Canadian patients and investigators to research in PBC that has positively shaped the field to date.

Statement from The Canadian Association for the Study of the Liver: The Canadian Association for the Study of the Liver believes that patients and their physicians should have access to a broad range of treatment options regardless of geographic location, financial status, treatment status or disease severity in order to ensure the best possible outcomes. It is up to physicians and their patients to make individual treatment decisions based on the needs of the patients.

7. Conflict of Interest Declarations

To maintain the objectivity and credibility of the CADTH drug review programs, all participants in the drug review processes must disclose any real, potential, or perceived conflicts of interest. This conflict of interest declaration is required for participation. Declarations made do not negate or preclude the use of the clinician group input. CADTH may contact your group with further questions, as needed. Please see the *Procedures for CADTH Drug Reimbursement Reviews* (section 6.3) for further details.

1. Did you receive help from outside your clinician group to complete this submission? If yes, please detail the help and who provided it.

   Administrative support only in collecting conflict of interests and collating opinions: Mr Robert Bick, Health Policy Consultant.

2. Did you receive help from outside your clinician group to collect or analyze any information used in this submission? If yes, please detail the help and who provided it.

   No

3. List any companies or organizations that have provided your group with financial payment over the past two years AND who may have direct or indirect interest in the drug under review. **Please note that this is required for <u>each clinician</u> who contributed**

to the input — please add more tables as needed (copy and paste). It is preferred for all declarations to be included in a single document.

Declaration for Clinician 1

Name: Gideon Hirschfield
Position: Lily and Terry Horner Chair in Autoimmune Liver Disease Research, UHN, Toronto and Co-PI CaNAL
Date: 9-12-2024

☒ **I hereby certify** that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Table 1: Conflict of Interest Declaration for Clinician 1

	Check appropriate dollar range*			
Company	**$0 to $5,000**	**$5,001 to $10,000**	**$10,001 to $50,000**	**In excess of $50,000**
Advanz			x	
Intercept			x	
Gilead/Cymabay			x	
Escient	x			
Ipsen			x	
GSK			x	
Pliant			x	
Mirum		x		
Kowa		x		
Falk		x		
(relates to Consultancy/Teaching/Advisory Boards for all above)				

* Place an X in the appropriate dollar range cells for each company.

The CaNAL research group is supported by philanthropy. As part of that philanthrophy beyond patient donations, UHN Foundation and the University of Edmonton has received unrestricted support in the last five years from Intercept, Advanz and Ipsen (>$50,000) for each party.

Declaration for Clinician

Name: Erin Kelly
Position: Assistant Professor, University of Ottawa
Date: 3/12/2024

☒ I hereby certify that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Table 2: Conflict of Interest Declaration for Clinician 2

	Check appropriate dollar range*			
Company	**$0 to $5,000**	**$5,001 to $10,000**	**$10,001 to $50,000**	**In excess of $50,000**
Ipsen		x		
Gilead		x		
Add or remove rows as required				

* Place an X in the appropriate dollar range cells for each company.

Declaration for Clinician

Name: Mark Swain
Position: Professor of Medicine
Date: 4/12/2024

☒ I hereby certify that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Table 2: Conflict of Interest Declaration for Clinician 2

	Check appropriate dollar range*			
Company	**$0 to $5,000**	**$5,001 to $10,000**	**$10,001 to $50,000**	**In excess of $50,000**
Novo Nordisk (advisory panel(			x	
Ipsen (advisory role)		x		
GSK (advisory role)	x			
Advanz (advisory role)	x			
Abbott (advisory role)			x	
Gilead (advisory role)	x			
Gilead, BMS, CymaBay, Intercept, Genfit, Pfizer, Novartis, Astra Zeneca, GSK, Celgene, Novo Nordisk, Axcella Health Inc., Merck, Galectin Therapeutics, Calliditas Therapeutics, Madrigal, AbbVie, Altimmune, Roche, Kowa, Ipsen, Intercept, 89Bio (Clinical trial or research support				X for each

Declaration for Clinician

Name: Andrew L Mason
Position: Prof. Medicine, University of Alberta
Date: 28 Nov 2024

☒ I hereby certify that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Table 2: Conflict of Interest Declaration for Clinician 2

	Check appropriate dollar range*			
Company	**$0 to $5,000**	**$5,001 to $10,000**	**$10,001 to $50,000**	**In excess of $50,000**
Gilead			X Payment as adviser	
Intercept	X Speaking engagements			
Ipsen	X Payment as adviser			X Research grant to CaNAL

* Place an X in the appropriate dollar range cells for each company.

Declaration for Clinician

Name: Julian Hercun
Position: Hepatologist, Centre hospitalier de l'Universite de Montreal, Montreal, QC.
Adjunct professor of medicine, University of Montreal, Montreal, QC.
Date: 27-11-2024

☒ I hereby certify that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Table 2: Conflict of Interest Declaration for Clinician 2

	Check appropriate dollar range*			
Company	**$0 to $5,000**	**$5,001 to $10,000**	**$10,001 to $50,000**	**In excess of $50,000**
Advanz			X	
Gilead		X		
Abbvie		X		
Ipsen		X		
GSK	X			
Lupin	X			

* Place an X in the appropriate dollar range cells for each company.

Declaration for Clinician

Name: Dr. Hin Hin KO
Position: Clinical Associate Professor
Date: 4/12/2024

☒ I hereby certify that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Table 2: Conflict of Interest Declaration for Clinician 2

Company	Check appropriate dollar range*			
	$0 to $5,000	$5,001 to $10,000	$10,001 to $50,000	In excess of $50,000
Advanz (speaker/advisor)	x			
Gilead (speaker/advisor)	x			
Ipsen (speaker/advisor)	x			

* Place an X in the appropriate dollar range cells for each company.

Name: Aliya Gulamhusein
Position: Toronto Centre For Liver Disease, UHN
Date: 10-12-2024

☒ I hereby certify that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Table 2: Conflict of Interest Declaration for Clinician 2

Company	Check appropriate dollar range*			
	$0 to $5,000	$5,001 to $10,000	$10,001 to $50,000	In excess of $50,000
Add company name	Advanz			
Add company name		Gilead		

* Place an X in the appropriate dollar range cells for each company.