Dear Sarah,



We have reviewed the draft evidence report for the evaluation of OCALIVA in primary biliary cholangitis (PBC). It is reassuring for patients that ICER consider that no further action is required to restrict patient access to OCALIVA since the annualized budget impact is 33% of ICERs threshold for a new drug.

However we have significant concerns regarding the economic modelling approach and assumptions considered in this assessment, which does not adequately reflect the progressive nature and disease severity of PBC nor the innovation that OCALIVA offers for patients who have an inadequate response to, or who are intolerant to UDCA. We look forward to continue working with you through the ongoing consultation process and provide our specific comments below to assist in amending the final report. Our comments are:

- 1. The ICER model omits UDCA intolerant PBC patients with the highest unmet medical need, for whom there is no other treatment option. PBC patients intolerant to UDCA have a worse prognosis than those with inadequate response to UDCA treatment. Although representing only ~ 3-4% of the entire PBC population, it remains a relevant group with high unmet need and should be included in the economic analysis of this orphan disease
- 2. The ICER model significantly underestimate the considerable human and financial costs associated with PBC disease progression if patients remain with elevated alkaline phosphatase (ALP). As a result of 25 calibrated transition probabilities determining patients' disease progression, the ICER model shows that instead of PBC patients progressing to clinical events (e.g. compensated and decompensated cirrhosis, HCC or liver transplant), they die from liver-related death

This is highlighted by considering the ICER model liver transplantation rate and comparing it with the UNOS database for US liver transplant. Intercept consider there are ~20,000 PBC patients with an inadequate response to or intolerant to UDCA in the US. The ICER model estimates that for 20,000 PBC patients, the cumulative number of cases over a 15 year period is as follows:

- a. 120 liver transplants (4/year)
- b. 1,000 decompensated cirrhotic cases (34/year)
- c. 800 HCC cases (27/year)
- d. 5,320 liver-related deaths (177/year)

The ICER model outputs are not reflective of the need for liver transplantation for PBC patients in the US. According to the UNOS database over a 15 year period (2000 to 2015) there were 2,912 transplants performed just for PBC as the primary reason for transplant (excludes HCC or cirrhosis as the primary reason). As of May 2016, 375 PBC patients were waitlisted for liver transplant in the US. If we consider other primary reasons like cirrhosis or HCC, the number of liver transplants required for PBC patients is even greater. This highlights the lack of PBC clinical disease progression in the ICER model, which results primarily in PBC patient deaths rather than clinical events or interventions, such as liver transplant. This ultimately leads to an undervaluation of the clinical effectiveness of OCALIVA in delaying or preventing PBC disease progression and clinical events.

3. ICER's model and assumptions are largely based on a classic hepatitis C virus (HCV) economic model structure although there are significant differences between HCV and PBC

- a. ICER's model structure is reflective of HCV focusing on histological progression with compensated cirrhosis being the precursor or "gatekeeper" for PBC disease progression. Patients must develop cirrhosis in order for PBC patients to progress, which is not the case clinically. For PBC, biochemical markers, rather than histological ones, are the key metrics that predict advanced disease progression. As such, there are relatively few papers adequately describing cirrhosis in PBC, which is markedly different from the HCV literature
- b. The ICER model fails to properly account for HCC development, because PBC patients may develop HCC from bile duct destruction without first transitioning to compensated cirrhosis
- c. PBC patients need to be able to transition to the liver transplant waitlist prior to developing HCC or decompensated cirrhosis. This is not possible in the ICER model, since patient must first develop compensated cirrhosis
- d. The ICER model omits a health state for PBC patients on liver transplant waitlists which is an important state. Critically, PBC patients often qualify as transplant candidates prior to developing HCC or decompensated cirrhosis, primarily driven by rising bilirubin which is highly predictive of a patient's imminent need for liver transplant
- e. The ICER model assumes patients who respond to UDCA 1 year post-treatment never experience PBC disease progression
- f. In the ICER model, the clinical effect of raised ALP and bilirubin does not seem to impact patients' immediate need for clinical intervention like liver transplant for example. It has been shown at EASL 2016 (Harms et al. 2016) that as soon as total bilirubin exceeds 1.6xULN, patients have an exponential risk progressing to liver transplant or death from a liver-related cause within only 19 months
- 4. The ICER model does not reflect the high risk of disease progression of the PBC patient population studied in the POISE trial if patients remain with elevated ALP
 - a. Specifically, the model considers all patients to be at equal risk, with 90% of patients entering the model in stage 1-3 and remaining stable for the entirety of their life without any change to patients' disease progression. This is not the case for PBC which is a progressive disease
 - b. The patients in the POISE trial are at higher risk than those in the ICER model; POISE patients had PBC for ~9 years with 70% of patients in stage 2-3
- 5. Reliance solely on published literature to inform the model and its data inputs in PBC were there has been no innovation for over 20 years has resulted in much of the data for OCALIVA as a new drug being omitted since it is confidential until publication in the POISE manuscript or only available as conference posters and presentations which have been rejected by ICER on quality grounds. In addition the lack of PBC expert opinion in order to inform some of the model assumptions is a weakness in the ICER model when published literature is scarce as is the case with most orphan diseases. There are relatively few PBC experts in the US and their inputs would have guided ICER model assumptions
- 6. The utility parameters do not appear to accurately reflect the well-being of PBC patients and undervalue the quality of life of PBC patients suffering from the most severe liver complications, i.e. decompensated cirrhosis, HCC and liver transplant. As a result, we believe the model underestimates the number of Quality Adjusted Life Years (QALYs) for both UDCA alone, and in combination with OCALIVA

- 7. The model takes the perspective of a third-party payer only, with no account for the lost productivity or societal costs from delaying PBC disease progression. This is a relevant omission given that patients are women of working age
- 8. The ICER model uses HCV-based cost estimates which do not reflect how PBC patients are managed, especially since compensated cirrhosis is only rarely documented in PBC
 - a. Patients with ALP > 1.67xULN and normal bilirubin are expected in the ICER model to have a similar management costs as HCV compensated cirrhotic patients
 - b. PBC patients with elevated bilirubin have more serious consequences that HCV cirrhotic patients. This includes more outpatient and inpatient visits than seen in HCV, because PBC patients' health is rapidly deteriorating. Assuming PBC patient management costs are similar to HCV compensated cirrhotic in the ICER model underestimates the cost of PBC disease management
 - c. The ICER cost associated with liver transplant is underestimated. The estimated average 2014 billed cost per liver transplant was \$739,100 (Milliman report). Buchanan et al. (2009), estimated the total cost to be at least \$424,600 (liver transplantation \$276,200, pre-transplant \$77,100 per year up to 2 days prior to liver transplant, and \$71,300 for post-transplant)

As a result, we believe the ICER model underestimates PBC disease management cost as well as the cost associated with avoiding or delaying liver transplant.

- 9. ICER have previously only reviewed non-orphan drugs. A willingness-to-pay threshold ranging from \$150,000 to \$300,000 would be more appropriate as the economic threshold for an orphan drug. We consider that OCALIVA should have a threshold above \$100,000, given that PBC is an orphan disease and that OCALIVA will be used for those patients inadequately controlled or intolerant to UDCA
 - a. WHO proposed developing countries to consider a cost-per-quality-adjusted life years (QALYs) gained of 2-3 times the gross domestic product per capita (Baltussen et al. 2002), i.e. \$110,000-\$165,000 (assuming a GDP per capita of \$55,000)
 - b. Braithwaite et al (2008) estimated society's willingness to pay to range between \$100,000 and \$300,000 per QALY gained when evaluating the incremental cost-effectiveness of health care improvements from 1950 to 2003. Hirth et al. (2000) estimated the threshold at \$430,000
- 10. Furthermore, given the paucity of data in this orphan disease and lack of input from experts supporting the ICER analysis, we have significant reservations regarding the validity of PBC disease progression in the ICER model. Even for OCALIVA in PBC, limited data has been included by ICER in determining the clinical comparative effectiveness of OCALIVA which has resulted in an underestimation of the value of OCALIVA in this disease. Intercept requested that the analysis be delayed to allow for the POISE manuscript to be shared; the POISE publication has been accepted for publication from a major medical journal and therefore cannot be shared without compromising the confidentiality of the data. We have also developed a cost-effectiveness model for OCALIVA in PBC in collaboration with US PBC and hepatology experts and look forward to sharing this with you in future consultations

Best regards

Rowena Holland PhD MBA VP Global Market Access Pricing and Reimbursement Two Pancras Square, 1st FL, Kings Cross, London, N1C 4AG T +44 (0)203 805 7549 M +44 (0)7468 725 97



Intercept

Dear Sarah,

As highlighted in your draft report for nonalcoholic steatohepatitis (NASH), we would like to reiterate that this economic review is premature to evaluate the clinical effectiveness of OCA (obeticholic acid) in this indication. A relevant analysis can only be conducted after the read out of our REGENERATE Phase 3 efficacy and safety data at the optimal dose, in the defined patient population with NASH and advanced fibrosis (F2/F3).

We acknowledge the unmet need among patients with NASH due to the lack of treatments. However, patients in need of treatment today with advanced fibrosis (F2/F3) should be encouraged to consult their physician to understand if they would be eligible for one of the ongoing clinical trials for OCA or any other drug being studied in NASH.

Best regards

Rowena Holland PhD MBA VP Global Market Access Pricing and Reimbursement Two Pancras Square, 1st FL, Kings Cross, London, N1C 4AG T +44 (0)203 805 7549 M +44 (0)7468 725 978 E rowena.holland@interceptpharma.com PATENT

June 9, 2016

Steven D. Pearson, MD, MSc, FRCP President Institute for Clinical and Economic Review One State Street, Suite 1050 Boston, MA 02109 USA

RE: ICER Review of Obeticholic Acid (OCA) for the treatment of Primary Biliary Cholangitis (PBC) and Nonalcoholic Steatohepatitis (NASH)

Dear Dr. Pearson:

Patients Rising is a Washington, DC-based non-profit organization with a very specific mission: we fight for access to vital therapies and services for all patients with life-threatening and chronic diseases. That is why Patients Rising is committed to speaking for patients as part of a balanced dialogue with providers, payers, policymakers and the advocacy community to address the complement of cost and access challenges Americans with serious diseases face today.

Clearly, one of the most pressing issues is improving access to, and reimbursement for, novel medicines that improve and extend people's lives. This is especially the case for patients with chronic liver diseases, such as primary biliary cholangitis (PBC) and non-alcoholic steatohepatitis (NASH), which can lead to liver failure and death if not adequately treated. Thus, Patients Rising signed onto the joint letter from the Global Liver Institute and other liver disease organizations that raises serious questions about the Institute for Clinical and Economic Review's draft reports on obeticholic acid (OCA) for the treatment of PBC and NASH.

Additionally, Patients Rising plans to join the Global Liver Institute in attending the CEPAC meeting in Portland on July 15th to raise our concerns that ICER's draft reports on OCA, which could have detrimental consequences for the estimated 130,000 Americans living with PBC and the approximately 30 million with NASH. Our specific concerns are summarized below.

1. Many Americans with PBC and NASH Have Few Treatment Options

In announcing accelerated approval of OCA on May 31, 2016 – five days after ICER announced its draft reports – the Food and Drug Administration's (FDA) presented a compelling argument for why this new therapy addresses an unmet need for patients. Although the only other treatment for PBC, ursodeoxycholic acid (UDCA), is effective in about 50 percent of patients, up to 40 percent do not achieve an adequate reduction in blood chemistries with UDCA, while 5-10 percent are unable to tolerate the therapy.

Of equal significance, FDA granted OCA orphan drug status due to the very small patient population for PBC and the fact that since UCDA was approved more than 20 years ago, there had been no other treatment option available. When FDA's Gastrointestinal Drugs Advisory Committee voted unanimously in April 2016 to recommend accelerated approval of obeticholic acid, committee members agreed that OCA fills an unmet need for patients with

rare and difficult liver diseases.

2. ICER Has Not Consulted with PBC and NASH Experts and Advocates Who Best Understand the Science and Limitations of UCDA

As documented at the Gastrointestinal Drugs Advisory Committee meeting in April, PBC is a rare and potentially fatal disease leading to liver failure and the need for a liver transplant in the 40-50 percent of patients who do not respond to UDCA. Yet, ICER conducted its assessments without appropriate patient participation in the clinical evaluation process and none of ICER's panel members has treated a PBC or NASH patient.

It is because the patient experience is absent that Patients Rising considers value frameworks – as they are currently being used in healthcare decision-making – as soulless backroom number crunching exercises. Obviously much can be garnered from study findings, and it appears ICER has gone to great lengths to qualify and quantify data for its evaluation. However, without considering value at the individual patient level, treatment options for rare diseases will be deemed too costly and access will be limited.

3. ICER's Clinical Effectiveness and Value Assessment of OCA Is Premature

When it comes to assessing the "value" of new drugs for orphan diseases like PBC, it is premature to even focus on a therapeutic category where there have been no new treatments in more than 20 years. Further, the only available evidence on OCA involves patients treated in clinical trials, which does not reflect the potential use of this new therapy in real-world practice.

This rush to evaluate a new medication that has yet to be prescribed and taken by eligible PBC patients raises the question of why ICER is moving forward quickly to estimate OCA's potential off-label use in treating NASH? The only conclusion is that ICER's report will be used by health plans to keep NASH patients from receiving this form of treatment, even though the disease can lead to cirrhosis, in which the liver is permanently damaged and scarred.

4. ICER's Model Will Impede Physicians' Clinical Judgement

No matter how much data is collected and analyzed, value assessments should not replace the clinical judgement of physicians treating the patient in front of them. Especially in the case where meaningful Phase III evidence is lacking, we must rely on the doctor's understanding of the differences among each patient and whether specific patients have co-morbidities or prior toxicities that must be taken into consideration, which no value framework can ever really assess.

5. Concerns About ICER's Cost Effectiveness Model

In both of ICER's draft reports, the organization makes an assumption about the cost for a year's worth of OCA treatment absent any list price at the time of this report. A \$65,000 list price is used for analysis, which ICER has deemed too high and has set a \$15,000 amount for overall fiscal sustainability. Yet, from our discussions with liver disease organizations, it is apparent ICER uses a different model for liver transplants where the average negotiated rate for insurers is used instead of an arbitrary list price off of a hospital charge master. Thus, if ICER is willing to use this real-world approach when analyzing the true estimated cost of a hospital procedure, the same parameters should apply to new drug treatments because insurance companies and pharmacy benefit manager rarely, if ever, pay a list price.

Additionally, we are aware that ICER has not taken into consideration the following factors when determining the cost of OCA:

- Additional competitive treatments entering the market
- Rebates provided by pharmaceutical companies to pharmacy benefit managers
- The drug going off-patent
- The cost to develop the medicine, which in this case is 14 years

Beyond these specific issues, the burning question for Patients Rising is why is ICER putting OCA under the microscope now? Is the goal to question the value for this new therapy before it even reaches patients so as to narrow utilization and therefore, limit costs to payers?

Like other advocates and healthcare stakeholders, we share ICER's concerns about the rising costs of care. Yet, what is in the best interest of all Americans is better ways to treat diseases so patients can live long and prosper – and not methods that devalue patients' needs for the sake of overall national sustainability.

Thank you in advance for considering our views.

Sincerely,

Tenny M. Wilcon

Terry Wilcox Co-Founder & Executive Director, Patients Rising

June 9, 2016

Steven Pearson, MD President Institute for Clinical and Economic Review

Dear Dr. Pearson,

We, as members of the liver community representing patients with primary biliary cholangitis (PBC), appreciate the opportunity to comment on the Institute for Clinical and Economic Review's (ICER) draft report on obeticholic acid (OCA) in PBC and non-alcoholic steatohepatitis (NASH) in preparation for the July 15 meeting of the Comparative Effectiveness Public Advisory Council (CEPAC). As liver community representatives we will attend the CEPAC meeting to present accurate information on the relevant diseases and call for more meaningful patient participation in the ICER process.

PBC is a rare, orphan disease, disproportionately affecting women, for which the introduction of OCA would result in the first effective treatment available to PBC patients in the last 20 years. The addition of OCA to limited available treatment options, is an eagerly awaited scientific and patient care advancement, potentially saving many lives since the majority of patients are either intolerant of or do not respond to current therapies.

It is important to emphasize that even though a majority of patients with PBC are asymptomatic at the time of initial diagnosis, most develop symptoms over time at varying rates. Since the majority of patients develop symptoms over time it is important not to overlook the progression of this debilitating disease and undermine the risk faced by PBC patients. Lack of symptoms does not equate to lack of disease progression or damage. It is also crucial to emphasize that with PBC, if left untreated, a significant portion of patients will experience liver failure, transplant, or death within 5 to 10 years. Whether asymptomatic or symptomatic, PBC is 1 of the top 10 most common causes of liver transplant and accounts for up to 2% of deaths from cirrhosis. Transplant is recommended before most PBC symptoms even occur. Recent studies suggest that about 30% of those diagnosed with PBC will require a liver transplant. The avoidance of up to 42,000 liver transplants from PBC alone impacts the entire transplant list of candidates and significantly lowers individual and societal health care costs. Since ursodeoxycholic acid (UDCA) became widely used for PBC, liver transplant rates have fallen in this population, reflecting a true change in natural history affected by a well-tolerated medication. OCA, only recently approved by the U.S. Food and Drug Administration, deserves the chance to be fully accessible to PBC patients and the impact then measured.

The hope that OCA will provide similar results for NASH patients is extremely high. NASH is a highly prevalent disease for which there are no effective medications. The potential benefit of OCA treatment for NASH patients would have an immeasurable positive impact on public health starting with the estimated 12% of the US population battling this complex illness. As early as 2020, NASH is expected to surpass hepatitis C as the leading cause of liver transplant in the US, and with donor shortages as a limiting factor we need more treatments and interventions to reduce liver related mortality and to improve individual quality of life. With the lack of approved

treatment for NASH it is crucial for drugs such as OCA to be appropriately and systematically tested by the appropriate government entities in a patient-centered process continuing innovation in liver disease drug development.

We do not contest ICER's right as an independent organization to perform and disseminate costeffectiveness assessments. However the choice of PBC, a rare disease, with few effective treatment options is disturbing. The choice to review NASH is premature since no new medication has been approved, let alone priced for this condition, so we are unclear why this condition has been included or how it could be fairly evaluated and so request that you remove it from review at this time.

We are also disappointed by the outlined process for public engagement, specifically the lack of patient and clinical subject matter experts included on voting panels, inadequate public comment periods, inadequate testimony periods at public meetings, and limited accessibility to the CEPAC meeting. Patients and advocates may find travel to Portland, ME, a barrier to participation in the public comment meeting. Overall, the process of public and patient engagement is contrary to the concepts of a patient-centered value-framework, such as those developed by the National Health Council. Any results of your current process will not, by definition, be patient-centered and accurately reflect the needs, perspective, or potential impact on individuals with liver disease and may significantly impede access to treatment.

We appreciate the opportunity to offer comments on this process. If you have any questions or wish to discuss this further, please contact Donna Cryer, at <u>dcryer@globalliver.org</u> or (202) 603-3493.

Sincerely,

Global Liver Institute Alliance for the Adoption of Innovations in Medicine (Aimed Alliance) American Liver Foundation Patients Rising PBCers Organization PBC Foundation Society for Women's Health Research

COMMENTS ON OCA IN PBC

Dear Sirs/Ladies

As you well know, there has not been much progress in decades in this disease entity. As it is, patients with cholestatic disorders have to reach a very advanced clinical deterioration before the hopes of receiving a liver transplant. In the interim, their quality of life dramatically suffers and this takes its toll on patients as well as caregivers and families

OCA is a major advance in terms of its effectiveness and its improvement in quality of life issues.

The models of cost-effectiveness should consider that this is a female predominant disease (versus HCV which is male predominant) and that the extra years of longevity may affect QALY calculations. Health utility scores may also not lend themselves to easy extrapolation. Both of these factors may adversely impact QALY and cost-effectiveness calculations of OCA in women

Thank you

Vinod K Rustgi, MD, MBA Professor of Medicine Clinical Chief of Gastroenterology/Director of Hepatology Robert Wood Johnson School of Medicine New Brunswick, NJ



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Florence P. Haseltine, PhD, MD Emerita Scientist, National Institutes of Health Founder Society for Women's Health Research Alexandria, VA June 9, 2016

Steven Pearson, MD President Institute for Clinical and Economic Review 2 Liberty Square, Ninth Floor Boston, MA 02109

Dear Dr. Pearson,

On behalf of the Society for Women's Health Research (SWHR®), we appreciate the opportunity to comment on the Institute for Clinical and Economic Review's (ICER) draft evidence report titled "Obeticholic Acid for the Treatment of Primary Biliary Cholangitis: Comparative Clinical Effectiveness and Value," in preparation for the meeting of the Comparative Effectiveness Public Advisory Council (CEPAC) in July.

SWHR, a national non-profit organization, located in Washington D.C., is widely recognized as the thought-leader in promoting research on biological differences in disease. For more than 25 years, our organization has brought attention to the variety of diseases and conditions that disproportionately or predominately impact women and is dedicated to transforming women's health through science, advocacy, and education.

Primary Biliary Cholangitis (PBC) is a chronic disease of the liver that slowly destroys the organ's medium-sized bile ducts. Research suggests that it is a rare autoimmune disease which appears to have a genetic component, but the underlying cause of the disease is currently unknown.

Additionally, PBC disproportionately affects women in the prime of their lives. Approximately 90 percent of PBC patients are women and the disease usually presents between the ages of 30-65; however, patients as young as 22 have been diagnosed. It is our hope that as the field of personalized medicine and genetics advances, and more attention and research is directed



at this disease, the underlying genetic components and causes can be identified, leading to improved diagnosis and treatments for patients.

Since the U.S. Food and Drug Administration (FDA) recently granted approval for Ocaliva (obeticholic acid) for the treatment of PBC in combination with ursodeoxycholic acid (UDCA) in adults with an inadequate response to UDCA, or as a single therapy in adults unable to tolerate UDCA, SWHR believes that ICER should consider this approval as they are evaluating the comparative effectiveness and value of this drug because of the significant benefit this therapy could have for women who suffer from this disease.

PBC is difficult to diagnose early, as patients are often asymptomatic in the initial stages of the disease. As the disease progresses, the most common symptoms are fatigue, itching, and dry mouth and eyes. Some individuals may experience jaundice, a condition that causes the skin and whites of the eyes to turn yellow. PBC is diagnosed in approximately 60 percent of people before symptoms begin and often ultrasounds and liber biopsies are required to aid in diagnosis. The hallmark trait of PBC is the presence of antimitochondrial antibodies (AMAs) in the blood. These AMAs can be found in 90-95 percent of PBC patients.

UDCA has been shown to slow the progression of the disease, and is presently the only treatment option available for PBC patients. In fact, there have not been any novel treatments for this disease in over three decades. Many patients experience resistance or intolerance to UDCA, leaving them no treatment option for managing this chronic condition, which may lead to life-threatening complications or require a transplant. Innovative therapies are desperately needed to improve the health and quality of life for PBC patients.

SWHR strongly believes that with FDA's recent approval of Ocaliva (obeticholic acid), ICER should evaluate the benefits that this therapy could have for PBC patients – especially women at the CEPAC meeting in July.

Thank you for the opportunity to provide comments on this draft evidence report. If you have any questions or would like to discuss this issue further, please contact me at <u>heather@swhr.org</u> or (202) 496-5003.

Sincerely,

Mather Barl

Heather Boyd, MPP Director of Public Policy Society for Women's Health Research (SWHR)