NYE METODER

Anmodning om vurdering av legemiddel i Nye metoder

Skjema for leverandører

En leverandør som ønsker offentlig finansiering av et legemiddel/legemiddelindikasjon i den norske spesialisthelsetjenesten, skal anmode om vurdering i Nye metoder ved å fylle ut dette skjemaet.

Utfylt anmodningsskjema sendes til Nye metoder: nyemetoder@helse-sorost.no

Leverandøren skal på anmodningstidspunktet både ha et forslag til type helseøkonomisk analyse og en plan for når de leverer dokumentasjonen. Merk at dokumentasjon i henhold til oppdraget fra Bestillerforum for nye metoder må leveres inn senest 12 måneder etter anmodningstidspunktet.

Hele anmodningsskjemaet skal fylles ut. Mer informasjon og veiledning finnes i artikkelen For leverandører (www.nyemetoder.no)

Merk: Skjemaet vil bli publisert i sin helhet på nyemetoder.no.

Innsender er klar over at skjemaet vil bli publisert i sin helhet (må krysses av): X

Fyll ut dato for innsending av skjema: Klikk eller trykk for å skrive inn en dato.

1 Kontaktopplysninger	
1.1 Leverandør (innehaver/søker av markedsføringstillatelse i Norge)	Ipsen AB
1.2 Navn kontaktperson	Anna Ovanfors
1.3 Stilling kontaktperson	Nordic Market Access Manager
1.4 Telefon	+46 070 244 47 97
1.5 E-post	anna.ovanfors@ipsen.com
Ekstern representasjon - vedlegg fullmakt	
1.6 Navn/virksomhet	N/A
1.7 Telefon og e-post	N/A

2 Legemiddelinformasjon og indikasjon	
2.1 Hva gjelder anmodningen? *Kryss av for hva anmodningen gjelder*	A new indication [X]
2.2 Hvilken indikasjon gjelder anmodningen? *Indikasjonen skal oppgis på norsk. Hvis prosess for godkjenning pågår, oppgi også indikasjon på engelsk.* *Merk: Leverandør skal anmode om vurdering av hele indikasjonen som de har fått godkjent eller søker om godkjenning for.* *Dersom leverandør foreslår en avgrensning til undergrupper, må dette begrunnes og leverandør må levere dokumentasjonen som trengs for å foreta en vurdering av undergruppen i tillegg til dokumentasjonen for hele indikasjonen.*	Norsk: Behandling av primær biliær kolangitt, i kombinasjon med UDCA eller som monoterapi hos pasienter som er intolerante mot UDCA, hos voksne som ikke er kvalifisert for behandling med fibrater. English: Treatment of primary biliary cholangitis, in combination with UDCA or as monotherapy in patients who are intolerant to UDCA, in adults who are ineligible for treatment with fibrates. Motivation: A patient population that is intolerant to UDCA or ineligible for treatment with fibrates would include patients already on statins who should not take bezafibrate, in addition to patients with kidney disease. These patients currently have no treatment option. Based on discussions with a Norwegian clinician, Kristin Kaasen Jørgensen at Akershus University Hospital, and the Norwegian Patient Registry 2023, we have the following estimation on the number of patients ineligible for treatment with bezafibrate: - 1125 pts: PBC prevalence - 923 pts: Diagnosis rate of 100% and 1st line treatment rate of 82% - 369 pts: 40% non-responders (2nd line eligible patients) - 111 pts: Patients ineligible for fibrates
2.3 Handelsnavn	Iqirvo
2.4 Generisk navn/virkestoff	Elafibranor
2.6 Administrasjonsform og styrke *Oppgi også forventet dosering og behandlingslengde* *Skriv kort*	Film-coated tablet for oral use
2.7 Farmakoterapeutisk gruppe og virkningsmekanisme. *Skriv kort*	Other drugs for bile therapy (A05AX). Elafibranor is a novel, first-in-class peroxisome proliferator-activated receptor (PPAR) α/δ co-agonist. PPARs are ligand-activated nuclear transcription factors, which play a key role in bile acid metabolism and inflammation. There are three PPAR isotypes (α, δ, and γ), of which elafibranor specifically activates two: PPARα and PPARδ [1, 2]. Due to its unique dual mechanism of action, elafibranor acts upon

	Complementary pathways in primary biliary cholangitis (PBC): - Activation of PPARα results in detoxification and excretion of bile acids, as well as inhibition of bile acid synthesis [2]. Together, these mechanisms reduce the concentration of bile acids in the liver and thereby reduce the level of hepatic damage due to cholestasis in patients with PBC [2,3]. - Activation of PPARδ leads to beneficial effects on bile homeostasis, including regulation of transport and absorption of bile compounds, and provides anti-fibrotic activity [4]. Moreover, PPARα and PPARδ activation has anti-inflammatory effects by acting on nuclear factor kappa B (NF-κB) and B-cell lymphoma 6 (BCL6) pathways [2, 5, 6]. In summary, elafibranor decreases bile output, bile toxicity, inflammation, and fibrosis.

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3 Historikk – virkestoff og indikasjon	
3.1 Har Nye metoder behandlet metoder med det aktuelle virkestoffet tidligere? Hvis ja, oppgi ID-nummer til metoden/metodene i Nye metoder	Yes ID-nummer: ID2024_024
3.2 Er du kjent med om andre legemidler/virkestoff er vurdert i Nye metoder til samme indikasjon? Hvis ja, oppgi ID-nummer til metoden/metodene i Nye metoder	NO
3.3 Er du kjent med om det er gjennomført en metodevurdering i et annet land som kan være relevant i norsk sammenheng? *Hvis ja, oppgi referanse*	NO No, not for the subgroup of patients who are ineligible for treatment with fibrates.

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4 Status for markedsføringstillatelse (MT) og markedsføring	
4.1 Har legemiddelet MT i Norge for en eller flere indikasjoner? Hvis ja - skriv inn dato for norsk MT for den første indikasjonen	The European Commission granted on 19 September 2024 a conditional marketing authorisation for Iqirvo in the following indication: “Iqirvo is indicated 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 patients unable to tolerate UDCA”.
4.2 Markedsføres legemiddelet i Norge?	NO
4.3 Har legemiddelet MT i Norge for anmodet indikasjon? For alle metoder: Fyll ut prosedyrenummer i EMA (det europeiske legemiddelbyrået) Hvis metoden ikke har MT i Norge, fyll ut forventet tidspunkt (måned/år) for CHMP opinion i EMA. Hvis metoden har MT i Norge, fyll ut dato for MT	Yes Prosedyrenummer i EMA: EMEA/H/C/0006231
4.4 Har legemiddelet en betinget markedsføringstillatelse for anmodet indikasjon? Hvis ja, fyll ut en beskrivelse av hva som skal leveres til EMA og når.	Yes In order to confirm the efficacy and safety of elafibranor in the treatment of PBC in combination with UDCA in adults with an inadequate response to UDCA, or as monotherapy in patients unable to tolerate UDCA, the marketing authorization holder (MAH) shall conduct and submit the final results of the phase III randomized, parallel-group, double-blind, placebo-controlled, two-arm study (ELFIDENCE) to evaluate the efficacy and safety of elafibranor on long-term clinical outcomes in adults with PBC. Due date: May 2030.
4.5 Har anmodet indikasjon vært i «accelerated assessment» hos EMA?	NO
4.6 Har legemiddelet «orphan drug designation» i EMA? *Hvis ja, fyll ut dato*	Yes FDA. Orphan Drug Designation and Approval: June 20, 2023 [49]. EMA. Public summary of opinion on orphan designation: June 20, 2023 [51].

5 Ordning for forenklet vurdering av PD-(L)1-legemidler	
5.1 Er legemiddelet registrert i Nye metoders ordning «Forenklet vurdering av PD-(L)1-legemidler"?	NO

6 Sammenlignbarhet og anbud	
6.1 Finnes det andre legemidler med lignende virkningsmekanisme og /eller tilsvarende effekt til den aktuelle indikasjonen?	Seladelpar has applied for reimbursement in Norway, but the application has been cancelled. Elafibranor is a novel, first-in-class peroxisome proliferator-activated receptor (PPAR) α/δ co-agonist. PPARs are ligand-activated nuclear transcription factors, which play a key role in bile acid metabolism and inflammation. There are three PPAR isotypes (α, δ, and γ), of which elafibranor specifically activates two: PPARα and PPARδ [1,2]. Due to its unique dual mechanism of action, elafibranor acts upon complementary pathways in primary biliary cholangitis (PBC): - Activation of PPARα results in detoxification and excretion of bile acids, as well as inhibition of bile acid synthesis [2]. Together, these mechanisms reduce the concentration of bile acids in the liver and thereby reduce the level of hepatic damage due to cholestasis in patients with PBC [2,3]. - Activation of PPARδ leads to beneficial effects on bile homeostasis, including regulation of transport and absorption of bile compounds, and provides anti-fibrotic activity [4]. - Moreover, PPARα and PPARδ activation has anti-inflammatory effects by acting on nuclear factor kappa B (NF-κB) and B-cell lymphoma 6 (BCL6) pathways [2,5,6]. In summary, elafibranor decreases both bile output, bile toxicity, inflammation, and fibrosis.
6.2 Vurderer leverandør at legemiddelet i anmodningen er sammenlignbart med et eller flere andre legemidler som Nye metoder har besluttet å innføre til den samme indikasjonen? Hvis ja, hvilke(t)? Oppgi ID-nummer på metoden/metodene i Nye metoder	NO Due to its unique dual mechanism of action, elafibranor acts upon complementary pathways in PBC, resulting in additional therapeutic benefits compared with other treatments on the market. For this reason, and since there exists no other treatment option in the subgroup of patients that are in-eligible to treatment with fibrates, we state that elafibranor should be compared according to ELATIVE: head-to-head treatment comparison vs. UDCA monotherapy/no treatment.
6.3 Er det eksisterende anbud på terapiområdet som kan være aktuelt for legemiddelet?	Yes The tender for "Sjeldne sykdommer" included Ocaliva before withdrawal from the market.

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7 Nordisk samarbeid JNHB (Joint Nordic HTA-bodies)	
7.1 Er anmodet indikasjon aktuell for utredning i det nordiske HTA-samarbeidet JNHB? Hvis nei, begrunn kort	NO Firstly, there are significant differences in national treatment standards and practices. Given these differences, it is deemed more suitable to tailor the approach to each national agency specifically. Secondly, reimbursement dossiers have already been submitted in the other Nordic countries.

8 Europeisk samarbeid om vurdering av relativ effekt og sikkerhet (HTAR)	
8.1 Er anmodet legemiddel/indikasjon omfattet av regelverket for utredning av relativ effekt og sikkerhet i europeisk prosess (HTAR)? Hvis ja, fyll ut dato for søknad om MT til EMA	NO

9 Helseøkonomisk dokumentasjon og forslag til helseøkonomisk analyse	
9.1 Hvilken type helseøkonomisk analyse foreslår leverandøren? F.eks. kostnad-per-QALY analyse eller kostnadsminimeringsanalyse. Begrunn forslaget	We propose that elafibranor undergoes a cost-utility analysis, a type C evaluation. No other evaluations have been done in patients with PBC who are ineligible for fibrates. Thus, cost-effectiveness should be established.
9.2 Pasientpopulasjonen som den helseøkonomiske analysen baseres på, herunder eventuelle undergrupper.	Treatment of primary biliary cholangitis, in combination with UDCA or as monotherapy in patients who are intolerant to UDCA, in adults who are ineligible for treatment with fibrates.
9.3 Hvilken dokumentasjon skal ligge til grunn? (H2H studie, ITC, konstruert komparatorarm etc.) Angi det som er relevant med tanke på hvilken type analyse som foreslås.	Head-to-head treatment comparison vs. UDCA monotherapy or no treatment.
9.4 Forventet legemiddelbudsjett i det året med størst budsjettvirkning i de første fem år.	Limited, to be included in submission.
9.5 Forventet tidspunkt (måned og år) for levering av dokumentasjon til Direktoratet for medisinske produkter og/eller Sykehusinnkjøp HF. Tidspunkt må oppgis	Augusti 31, 2025

10 Sykdommen og eksisterende behandling	
10.1 Sykdomsbeskrivelse for aktuell indikasjon Kort beskrivelse av sykdommens patofysiologi og klinisk presentasjon / symptombilde, eventuelt inkl. referanser	PBC is a rare, progressive, chronic autoimmune disease of the liver, characterized by the slow destruction of small intrahepatic bile ducts [3,7]. This prevents the flow of bile, causing it to build up in the liver in a process known as cholestasis, which leads to scarring of the liver (fibrosis) and can progress to severe scarring (cirrhosis), liver failure, and death [3]. Many patients with PBC are asymptomatic at diagnosis but usually accumulate a range of symptoms and comorbidities as the disease progresses [3,8,9]. These include pruritus, fatigue, bone ache, depression, and cognitive dysfunction, with pruritus (itching) and fatigue being the most common symptoms, affecting up to 70% and 80% of patients, respectively [10-13]. End-stage PBC is associated with progressive jaundice, malnutrition, portal hypertension, and liver failure, which can lead to premature death in the absence of a liver transplant [14]. Patients with PBC experience a significant humanistic burden from diagnosis through to end-stage disease, and the high symptom burden can significantly impact both patients' health-related quality of life (HRQoL) as well as the ability to perform activities of daily living [15,16].
10.2 Fagområde Angi hvilket fagområde som best beskriver metoden	Immunology
10.3 Kreftområde Hvis metoden gjelder fagområdet Kreftsykdommer, angi hvilket kreftområde som er aktuelt	No cancer disease
10.4 Dagens behandling Nåværende standardbehandling i Norge, inkl. referanse	UDCA is the only available first-line treatment for PBC, and the backbone of later lines of treatment. Several qualitative scoring systems have been developed to assess biochemical response to treatment in patients with PBC, of which both the Paris-II and Toronto scoring systems are used in Norway [3]. In some hospitals, response is assessed using other sets of criteria (which are all in accordance with the European Association for the Study of the Liver [EASL] Clinical Practice Guidelines for PBC) [3]. There is no consensus definition for an "inadequate response", but regardless of the response criteria/definition used, the response assessment is generally done after 1 year. If the patient's response to UDCA is evaluated as positive, the patient continues with regular follow-up visits. However, up to 5% of patients are intolerant to UDCA, and about 30-40% of PBC patients in Norway would be assessed to have an inadequate response to first-line UDCA (depending on the response definition used) [17-19].

	The effect and safety of bezafibrate in PBC has been studied in a phase 3, randomized, double-blind, placebo-controlled trial (BEZURSO) (5), and the requirement for scientifically documented effect is met when the drug is administered in combination with ursodeoxycholic acid (3). Bezafibrate is a PPAR agonist. However, as off-label treatments, fibrates are not approved for the treatment of PBC by any regulatory bodies and are also associated with safety limitations. Fibrates may lead to creatinine elevation, raising concerns about nephrotoxicity, and approximately 5–10% of patients, especially those on bezafibrate, experience musculoskeletal pain. Both fenofibrate and bezafibrate are contraindicated in those with renal impairment, as well as those with hepatic impairment for bezafibrate and those with active liver disease for fenofibrate. Further, the efficacy of bezafibrate is limited in patients with portal hypertension, and those with cirrhosis have high discontinuation rates with fenofibrate. For patients who have an inadequate response to or do not tolerate UDCA who also are ineligible for treatment with fibrates, there currently do not exist any treatment options. It is important with treatment options for patients with PBC who do not respond adequately to treatment and so progress to cirrhosis and liver failure, since liver transplantation is currently the only remaining treatment option available to prevent premature death [21].
10.5 Prognose Beskriv prognosen med nåværende behandlingstilbud, inkl. referanse	Delayed diagnosis, which occurs in approximately 25% of cases, negatively impacts PBC prognosis, as patients with a delayed diagnosis are likely to have later-stage PBC than those with an earlier diagnosis and may therefore be more difficult to treat [22]. About 30-40% of PBC patients in Norway would be assessed to have an inadequate response to first-line UDCA (depending on the response definition used), leaving them at increased risk of disease progression and further complications [18,19]. Studies have shown that UDCA does not improve outcomes such as all-cause mortality, liver transplantation, or serious complications or comorbidities [8,23,24]. For patients who do not adequately respond to currently available treatments and progress to cirrhosis and severe disease or suffer with severe medically resistant pruritus, liver transplant is required [3]. The outcomes of liver transplants are usually favorable, with 5-year patient survival rates of 80–85%. However, symptoms of PBC, including fatigue, often persist after transplant. Recurrence of PBC has also been reported in patients receiving a liver transplant; following orthotopic liver transplant, recurrent PBC is estimated to occur in 9–35% of individuals within

	1.6–6.5 years [26]. As PBC advances, patients may also develop complications such as hepatocellular carcinoma (HCC), for which there are very limited effective treatments to improve survival [27]. Data from a historical UK cohort (N=770) suggests that the average survival of patients with PBC receiving no or suboptimal treatment is approximately 10 years from presentation, with 26% of patients developing liver failure within 10 years of diagnosis [28]. Overall 5-year survival and transplant-free survival were also lower in people with cirrhosis compared with those without (80% vs. 93% for both estimates) [29]. A variety of biochemical markers are used to assess treatment response and disease progression in PBC, including [3]: - Alkaline phosphatase (ALP): increased values associated with disease progression. - Aspartate aminotransferase (AST)/alanine aminotransferase (ALT): markers of liver inflammation; a higher AST/ALT ratio is associated with an increased risk of future major hepatic complications, including autoimmune hepatitis. - Bilirubin: elevation at late stages; indicative of cirrhosis. ALP and total bilirubin (TB) are the key biomarkers and, when combined, are powerful predictors of cholestatic injury and liver function, transplant-free survival, and the speed of PBC progression [30,31]. A 2014 meta-analysis investigated ALP and bilirubin as surrogate endpoints in PBC, using data from 4,845 patients primarily treated with UDCA, with a median follow-up of 7.3 years [31]. Levels of both ALP and bilirubin, measured at study enrollment and each year for five years, were strongly associated with clinical outcomes, with combined assessment of both ALP and bilirubin levels being the strongest predictor of transplant-free survival duration [31]. High bilirubin levels are generally indicative of poorer outcomes, such as cirrhosis development and decreased survival in PBC, making bilirubin particularly useful as a marker of disease severity [3, 32]. Data from a Swedish population-based cohort support an increased risk of death in those with PBC compared to those without and highlight differences by gender; only 37% of men and 59% of women were alive 10 years after their PBC diagnosis. This study also found that the highest risk of death was observed in the first year after PBC diagnosis, with an HR of 9.04 (95% CI: 8.12, 10.07) for patients with PBC compared to patients without PBC [47].
10.6 Det nye legemiddelets innplassering i behandlingsalgoritmen	Elafibranor (in combination with UDCA, or as monotherapy in patients who are intolerant to UDCA) is expected to be placed as the treatment of choice for PBC in adults that are ineligible to treatment with fibrates.

10.7 Pasientgrunnlag *Beskrivelse, insidens og prevalens av pasienter omfattet av aktuell indikasjon* i Norge, inkl. referanse.* *Antall norske pasienter antatt aktuelle for behandling med legemiddelet til denne indikasjonen.* ** Hele pasientgruppen som omfattes av aktuell indikasjon skal beskrives*	Most patients present with PBC between 40 and 60 years of age; however, cases have been reported in individuals as young as 15 years [10, 33]. PBC is more common in female individuals than males (9:1 female: male ratio); however, male patients tend to have more advanced disease at diagnosis, likely due to delayed presentation [3,8,10]. PBC is a rare disease. In Norway, the prevalence of PBC is estimated to be 216/million (1,166 patients), and the incidence is estimated to be 18/million/year (97 patients/year), calculated using average prevalence and incidence estimates from Sweden, Finland, and Denmark [34-36]. The size of the patient population covered by the second-line PBC indication for elafibranor depends on the criteria used to assess the response to first-line treatment, as described in the "Current treatment" section. Based on discussions with a Norwegian clinician, Kristin Kaasen Jørgensen at Akershus University Hospital, and the Norwegian Patient Registry 2023, we have the following estimation on the number of patients being ineligible for treatment with bezafibrate: - 1125 pts: PBC prevalence - 923 pts: Diagnosis rate of 100% and 1st line treatment rate of 82% - 369 pts: 40% non-responders (2nd line eligible patients) -111 pts: fibrate-ineligible patients

11 Studiekarakteristika for relevante kliniske studier			
	Studie 1	Studie 2	Studie 3
11.1 Studie-ID Studienavn, NCT-nummer, hyperlenke	ELATIVE: A Double-blind, Randomized, Placebo-Controlled Study and Open-label Long-Term Extension to Evaluate the Efficacy and Safety of Elafibranor 80 mg in Patients With Primary Biliary Cholangitis With Inadequate Response or Intolerance to Ursodeoxycholic Acid. NCT04526665 https://clinicaltrials.gov/study/NCT04526665		
11.2 Studietype og -design	Phase III, a randomized, double-blind, placebo-controlled, parallel-group study, followed by an open-label long-term extension (LTE). The double-blind period comprised two parts. In part one, patients were randomly assigned to receive elafibranor or placebo for at least 52 weeks. In part two, patients continued their assigned regimen after week 52 until all patients had completed their week 52 assessment or for a maximum of 104 weeks, whichever came first. At the end of the double-blind period, patients could enter an open LTE period and receive elafibranor for up to 5 additional years [37].		
11.3 Formål	To evaluate the efficacy and safety of elafibranor in patients with PBC and inadequate response or intolerance to UDCA.		
11.4 Populasjon Viktige inklusjons- og eksklusjonskriterier	A total of 161 patients underwent randomization in a 2:1 ratio (108 patients were assigned to receive elafibranor, and 53 were assigned to receive placebo) [37]. Key inclusion criteria [38]: - Males or females aged 18-75 years inclusive - PBC diagnosis - UDCA for at least 12 months prior to screening and at stable dose for ⩾3 months, or unable to tolerate UDCA treatment - ALP ⩾1.67 x upper limit of normal (ULN) (different ULN values for females and males) - TB ⩽2 x ULN Key exclusion criteria [38]: - History or presence of other concomitant liver disease - History of: - Liver transplant, or current placement on liver transplant list - Model for end-stage liver disease-Sodium (MELD-Na) score ⩾12 - Patients with cirrhosis/portal hypertension complications - Hepatorenal syndrome - Markers of liver damage, such as: - ALT and/or AST >5 x ULN - Platelet count <150 x 103/µL - Albumin <3.0 g/dL		

	- Severely advanced patients according to Rotterdam criteria (TB >ULN and albumin <lower limit of normal [LLN]) - Prohibited medications: - Fibrates and glitazones (2 months prior to screening) - Ocaliva, azathioprine, colchicine, cyclosporine, methotrexate, mycophenolate mofetil, pentoxifylline, budesonide and other systemic corticosteroids (3 months prior to screening) - Immunotherapy directed against interleukins or other cytokines or chemokines (12 months prior to screening)		
11.5 Intervensjon (n) *Dosering, doseringsintervall, behandlingsvarighet*	80 mg elafibranor once daily (patients who were receiving a stable dose of UDCA at baseline were allowed to continue their concurrent UDCA treatment during the study) [37].		

11.7 Endepunkter Primære, sekundære og eksplorative endepunkter, herunder definisjon, målemetode og ev. tidspunkt for måling	Primary endpoint: biochemical response at week 52, defined as ALP level <1.67 x ULN, with a decrease of ⩾15% from baseline, and TB ⩽ULN. Key secondary endpoints include [37]: - Normalization of ALP level at week 52. - Pruritus intensity change from baseline through week 52 and through week 24, assessed using the PBC Worst Itch Numeric Rating Scale (WI-NRS) among patients with moderate-to-severe pruritus (defined as a WI-NRS score of ⩾4 at baseline); patients are asked to rate their worst itch over the past 24 hours on a scale ranging from zero (no itch) to 10 (worst itch imaginable) [39]. Other secondary endpoints include [37, 38]: - Change from baseline to week 52 in 5D-Itch; patients are asked to rate their symptoms in terms of 5 domains: degree, duration, direction (improvement or worsening), disability (effect on daily activities), and distribution of itching over the preceding 2-week period on a 1 to 5 scale, with 5 being the most affected. Total scores range from 5 (no pruritus) to 25 (most severe pruritus), with higher scores indicating worse itch-related quality of life [40]. - Change from baseline to week 52 in PBC-40; this questionnaire includes 40 questions that evaluate patients' experience across six domains: fatigue, emotional impact, social impact, cognitive function, general symptoms, and itch. Each question is scored from 1 to 5, then summed to give a total domain score. High scores represent high impact, and low scores low impact of PBC on quality of life (QoL) [41].-		

	Change from baseline in ALP level at 4, 13, 26, 39 and 52 weeks. - Change from baseline to week 52 in lipid parameters. - Proportion of patients with no worsening of pruritus from baseline through week 52 and through week 24 as measured by PBC WI-NRS. - Change from baseline to week 52 in immune response as measured by immunoglobulin (Ig)G and IgM. - Change from baseline to week 52 in bile acids and biomarkers of bile acid synthesis as measured by bile acids, serum 7-α-hydroxy-4-cholesten-3-one (C4) and fibroblast growth factor 19 (FGF-19). - Safety events, including treatment-emergent AEs (TEAEs) of different frequencies and severities, and adverse events of special interest (AESIs). A full list of ELATIVE trial endpoints is available in reference [38].		
11.8 Relevante subgruppeanalyser Beskrivelse av ev. subgruppeanalyser	- Age (<65, ⩾65) - ALP level at baseline >3 x ULN (Yes/No) - Advanced disease stage, defined as liver stiffness at baseline >10.0 kPa and/or bridging fibrosis or cirrhosis on histology (Yes/No) A full overview of subgroup analyses in the ELATIVE trial is available in reference [38].		
11.9 Oppfølgingstid Hvis pågående studie, angi oppfølgingstid for data som forventes å være tilgjengelige for vurderingen hos Direktoratet for medisinske produkter samt den forventede/planlagte samlede oppfølgingstid for studien	52 weeks (study is ongoing). In the LTE period, patients can receive elafibranor for up to 5 additional years [37].		

11.10 Tidsperspektiv resultater Pågående eller avsluttet studie? Tilgjengelige og fremtidige datakutt	Study started: 24-09-2020 Study primary completion: 01-06-2023 Study completion (estimated): December 2028		
11.11 Publikasjoner Tittel, forfatter, tidsskrift og årstall. Ev. forventet tidspunkt for publikasjon	Efficacy and Safety of elafibranor in Primary Biliary Cholangitis. Kowdley KV, et al. New Engl J Med. 2023 [37,38]		
11.12 Comparator. *Dosage, dosing interval, duration of treatment*	Placebo (patients who were receiving a stable dose of UDCA at baseline were allowed to continue their concurrent UDCA treatment during the study) [37].		

12 Igangsatte og planlagte studier

12.1 Er det pågående eller planlagte studier for legemiddelet innenfor samme indikasjon som kan gi ytterligere informasjon i fremtiden? Hvis ja, oppgi forventet tidspunkt	Yes The ELATIVE trial is ongoing. In addition to ELATIVE, a Phase III study of elafibranor in PBC began in August 2023 (ELFIDENCE; NCT06016842), evaluating the clinical efficacy and safety of elafibranor 80 mg on long-term outcomes [42].
12.2 Er det pågående eller planlagte studier for legemiddelet for andre indikasjoner?	Yes A Phase II trial with 12 weeks follow up is published and a long-term extension, 96 weeks, is ongoing [43,48].

13 Diagnostikk

13.1 Vil bruk av legemiddelet til anmodet indikasjon kreve diagnostisk test for analyse av biomarkør? Hvis ja, fyll ut de neste spørsmålene	NO
13.2 Er testen etablert i klinisk praksis? Hvis ja, testes pasientene rutinemessig i dag?	N/A
13.3 Hvis det er behov for en test som ikke er etablert i klinisk praksis, beskriv behovet inkludert antatte kostnader/ressursbruk	N/A

14 Andre relevante opplysninger	
14.1 Har dere vært i kontakt med fagpersoner (for eksempel klinikere) ved norske helseforetak om dette legemiddelet/indikasjonen? Hvis ja, hvem har dere vært i kontakt med og hva har de bidratt med? (Relevant informasjon i forbindelse med rekruttering av fageksperter i Nye metoder)	Yes. Kristin Kaasen Jørgensen, Akershus University Hospital, has participated in an advisory board focused on PBC in Norway.
14.2 Anser leverandør at det kan være spesielle forhold ved dette legemiddelet som gjør at en innkjøpsavtale ikke kan basere seg på flat rabatt for at legemiddelet skal kunne oppfylle prioriteringskriteriene? Hvis ja, begrunn kort. Hvis ja, skal eget skjema fylles ut og sendes til Sykehusinnkjøp HF samtidig med at dokumentasjon til metodevurdering sendes til Direktoratet for medisinske produkter. Nærmere informasjon og skjema: Informasjon og opplæring - Sykehusinnkjøp HF	NO
14.3 Andre relevante opplysninger?	References: [1] Cariou B, Zair Y, Staels B, et al. Diabetes Care. 2011;34:2008-14. [2] Ye X, Zhang T, Han H. Front Pharmacol. 2022;13:916866. [3] EASL. J Hepatol. 2017;67:145-72. [4] Wetten A, Jones DEJ, Dyson JK. Expert Opin Investig Drugs. 2022;31:1101-7. [5] Lee C-H, Chawla A, Urbiztondo N, et al. Science. 2003;302:453-7. [6] Pawlak M, Baugé E, Bourguet W, et al. Hepatology. 2014;60:1593-606. [7] Lindor KD, Bowlus CL, Boyer J, et al. Hepatology. 2019;69:394-419. [8] Hirschfield GM, Chazouillères O, Cortez-Pinto H, et al. Expert Rev Gastroenterol Hepatol. 2021;15:929-39. [9] Kim KA, Ki M, Choi HY, et al. Aliment Pharmacol Ther. 2016;43:154-62. [10] Galoosian A, Hanlon C, Zhang J, et al. J Clin Transl Hepatol. 2020;8:49-60. [11] Shaheen AA, Kaplan GG, Almishri W, et al. PLoS One 2018;13:e0194839. [12] Jung HE, Jang JY, Jeong SW, et al. Clin Mol Hepatol. 2012;18:375-82. [13] Milovanovic T, Popovic D, Stojkovic Lalosevic M, et al. Dig Dis. 2020;38:515-21. [14] Montano-Loza AJ, Corpechot C. Clin Gastroenterol Hepatol. 2021;19:2241-51 e1. [15] Mells GF, Pells G, Newton JL, et al. Hepatology. 2013;58:273-83. [16] Selmi C, Gershwin ME, Lindor KD, et al. Hepatology. 2007;46:1836-43.

	[17] Invernizzi P, Floreani A, Carbone M, et al. Dig Liver Dis. 2017;49:841-6. [18] Jørgensen KK. Primær biliær cholangitt – sjelden sykdom med nytt navn. Gastroenterologen. 20 Oct, 2017. Available at: https://gastroenterologen.no/2017/10/primaer-biliaer-cholangitt-sjelden-sykdom-med-nytt-navn/ [19] Henriksson I, Udumyan R, Nilsson E, et al. Scand J Gastroenterol. 2023;58:70-75. [20] Felleskatalogen.no. Ocaliva «Advanz Pharma». 25 Jul, 2022. Available at: https://www.felleskatalogen.no/medisin/ocaliva-advanz-pharma-631817 [21] Harms MH, Janssen QP, Adam R, et al. Aliment Pharmacol Ther. 2019;49:285-295. [22] Terziroli Beretta-Piccoli B, Stirnimann G, Cerny A, et al. Clin Rev Allergy Immunol. 2018;54:295-306. [23] Rudic JS, Poropat G, Krstic MN, et al. Cochrane Database Syst Rev 2012;12:Cd000551. [24] Setsu T, Yokoyama J, Takamura M, et al. J Hepatol 2020;73. [25] Nevens F, Andreone P, Mazzella G, et al. N Engl J Med 2016;375:631-43. [26] Silveira MG, Talwalkar JA, Lindor KD, et al. Am J Transplant. 2010;10:720-6. [27] Karaman B, Battal B, Sari S, et al. World J Gastroenterol. 2014;20:18059-60. [28] Prince M, Chetwynd A, Newman W, et al. Gastroenterology. 2002;123:1044-51. [29] Axley P, Mudumbi S, Sarker S, et al. PLoS One. 2018;13:e0197117. [30] FDA. Table of Surrogate Endpoints That Were the Basis of Drug Approval or Licensure. 28 Feb, 2022. Available at:https://www.fda.gov/drugs/development-resources/table-surrogate-endpoints-were-basis-drug-approval-or-licensure [31] Lammers WJ, van Buuren HR, Hirschfield GM, et al. Gastroenterology. 2014;147:1338-49 e5; quiz e15. [32] Hirschfield GM, Dyson JK, Alexander GJM, et al. Gut. 2018;67:1568-94. [33] Dahlan Y, Smith L, Simmonds D, et al. 2003;125:1476-9. [34] Lleo A, Jepsen P, Morenghi E, et al. Sci Rep. 2016;6:25906. [35] Marschall HU, Henriksson I, Lindberg S, et al. Sci Rep. 2019;9:11525. [36] Rautianen H, Salomaa V, Niemelå S, et al. Scand J Gastro. 2007;42:1347-53. [37] Kowdley KV, Bowlus CL, Levy C, et al. N Engl J Med. 2023;Online ahead of print. [38] Kowdley KV, Bowlus CL, Levy C, et al. N Engl J Med. 2023;Online ahead of print (Suppl.App.).

	[39] Schattenberg J, Williams B, Sowell F, et al. EASL 2023 Poster (THU-324). J Hepatol. 2023:78(Suppl 1);S955, 2023. [40] Elman S, Hynan LS, Gabriel V, et al. Br J Dermatol. 2010;162:587-93. [41] Jacoby A, Rannard A, Buck D, et al. Gut. 2005;54:1622-9. [42] Clinicaltrials.gov. A Long-Term Study of Elafibranor in Adult Participants With Primary Biliary Cholangitis (ELFIDENCE). Jan 31, 2024. Available at: https://clinicaltrials.gov/study/NCT06016842?intr=Elafibranor&viewType=Table&page=2&rank=16. [43] Clinicaltrials.gov. A Study to Assess Safety and Effectiveness of Elafibranor in Adult Participants With Primary Sclerosing Cholangitis (ELMWOOD). Jan 31, 2024. Available at: https://clinicaltrials.gov/ct2/show/NCT05627362. [44] Bahar R, Wong KA, Liu CH, et al. Gastroenterol Hepatol (N Y). 2018;14:154-63. [45] European Medicines Agency. Report of the stakeholder interaction meeting on the development of medicinal products for chronic noninfectious liver diseases (PBC, PSC, NASH). 2019. European Medicines Agency, London, December 3, 2018. Available at: https://www.ema.europa.eu/en/documents/report/report-european-medicines-agency-stakeholder-interaction-development-medicinal-products-chronic-non-infectious-liver-diseases-pbc-psc-nash_en.pdf [46] Murillo Perez, C.F., et al. Am J Gastroenterol. 2020;115:1066-1074. [47] Marschall H-U, et al. Sci Rep. August 8, 2019. Available at: https://pmc.ncbi.nlm.nih.gov/articles/PMC6687809/pdf/41598_2019_Article_47890.pdf [48] Levy C, et al J Hepatol. 2025. May 8:S0168-8278(25)00252-1 [49]FDA. Orphan Drug Designations and Approvals: elafibranor. Available at: https://www.accessdata.fda.gov/scripts/opdlisting/oopd/detailedIndex.cfm?cfgridkey=693919. Last accessed: 20th June 2023. [50]GENFIT. GENFIT announces FDA Grant of Breakthrough Therapy Designation to Elafibranor for the Treatment of PBC (18th April 2019). Available at: https://ir.genfit.com/news-releases/news-release-details/genfit-announces-fda-grant-breakthrough-therapy-designation. Last accessed: 20th June 2023. [51]EMA. Public summary of opinion on orphan designation: Elafibranor for the treatment of primary biliary cholangitis. . Last accessed: 20th June 2023.