National Institute for Health and Care Excellence

Health Technology Evaluation

Norucholic acid for treating primary sclerosing cholangitis ID6583
Response to stakeholder organisation comments on the draft remit and draft scope

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Comment 1: the draft remit and proposed process

Section	Stakeholder	Comments [sic]	Action
Appropriateness of an evaluation and proposed evaluation route	Dr. Falk (company)	The topic and proposed evaluation route are appropriate.	Thank you for your comment. No action required.
	Genetic Alliance UK	Genetic Alliance UK welcomes the opportunity to comment on the draft scope for norucholic acid (NA) to treat the rare condition primary sclerosing cholangitis (PSC). To our understanding, and from speaking with Genetic Alliance UK's member organisation, PSC Support, the proposed routing for this evaluation is appropriate.	Thank you for your comment. No action required.
	PSC Support	The evaluation of norucholic acid for PSC is highly appropriate given the current lack of licensed therapeutic options and the significant burden of the disease for patients. We support the proposed Single Technology Appraisal (STA) route. While PSC is a rare disease with a UK prevalence of approximately 6.12 per 100,000, the STA route is appropriate as norurcholic acid is likely to be used	Thank you for your comment. No action required.

Section	Stakeholder	Comments [sic]	Action
		across the broad PSC population rather than being restricted to a subgroup that might be rare enough for a Highly Specialised Technologies evaluation.	
Wording	Dr. Falk (company)	Yes, the remit is appropriate.	Thank you for your comment. No action required.
	PSC Support	The remit is acceptable in principle but should capture the reality of PSC. We suggest: To appraise the clinical and cost effectiveness of norucholic acid within its marketing authorisation for treating primary sclerosing cholangitis, including its impact on disease progression, health-related quality of life (HRQoL), and the prevention/reduction of end-stage liver disease complications.	Thank you for your comment. The remit uses standard wording, but where relevant and appropriate, impact of the condition and technology on the condition will be considered in the appraisal.
Timing Issues	Dr. Falk (company)	Timely reimbursement of norucholic acid (NCA) is important due to the high unmet need in PSC, a progressive condition associated with substantial morbidity and mortality for which no licensed therapies exist and for which off-label UDCA use has not demonstrated meaningful effects on disease progression or long-term histological outcomes. Furthermore, as PSC is a rare disease, timely access to NCA would be consistent with priority 4 of the UK Rare Diseases Framework, as reflected in England's Rare Diseases Action Plan 2025, which prioritises improved access to specialist care, treatment and drugs for people living with rare conditions [1]. References	Thank you for your comment. The appraisal will follow scheduled timelines.

Section	Stakeholder	Comments [sic]	Action
		1. England Rare Diseases Action Plan 2025: main report https://www.gov.uk/government/publications/england-rare-diseases-action-plan-2025/england-rare-diseases-action-plan-2025-main-report#executive-summary	
	Genetic Alliance UK	There are currently no effective licensed treatments for PSC in the UK, meaning a number of people progress to advanced liver disease and require liver transplantation. PSC is also one of the leading indications for liver transplant, despite its rarity, reflecting the severity of the condition. In addition, people with PSC live with a significant and ongoing increased risk of aggressive cancers which are often difficult to detect early and associated with poor outcomes. For these reasons, people with the condition are required to undergo frequent targeted screening. Even following transplant, recurrence occurs in a substantial proportion of people living with PSC. More information about complications is available on PSC Support's webpages here: https://pscsupport.org.uk/cancer/ https://pscsupport.org.uk/complications-in-psc/ We'd also like to signpost this helpful overview of the reasons for intensive monitoring of people living with PSC for cancer by the Liver Fellow Network: https://www.aasld.org/liver-fellow-network/core-series/why-series/why-do-people-primary-sclerosing-cholangitis-require-so Taken together, this highlights a clear unmet clinical need for this population and the urgent of timely evaluation of potential disease-modifying therapies for this condition.	Thank you for your comment. The appraisal will follow scheduled timelines.

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	PSC Support	PSC represents one of the most significant areas of unmet clinical need in hepatology and there is an urgent need to evaluate norucholic acid because: 1) There are currently no licensed disease-modifying therapies available. PSC was formally identified as a Top 10 research priority for liver and gallbladder disorders in the UK through a James Lind Alliance Priority Setting Partnership 2) PSC is one of the leading indications for liver transplant in the UK (10–15% of all UK liver transplant activity), despite being rare. A treatment that could delay or prevent progression to liver failure would reduce the need for transplants and unplanned hospital admissions. PSC recurs in approximately 20-30% of individuals post-transplant resulting in graft loss. This means that transplantation is not a cure or fix, is something that leads to a lifelong cycle of high-cost monitoring and potentially the need for re-transplantation. 3) PSC confers a higher risk of aggressive cancers than the general population. Up to 50% of cholangiocarcinoma cases are diagnosed within the first year of a PSC diagnosis. Early treatment has the potential to alter this.	Thank you for your comment. The appraisal will follow scheduled timelines.
Additional comments on the draft remit		No comments	

Comment 2: the draft scope

Section	Consultee/ Commentator	Comments [sic]	Action
Background information	Dr. Falk (company)	The background information would benefit from amendment to better reflect the nature, progression and long-term consequences of PSC, and to accurately describe the limitations of UDCA.	Thank you for your comment. The background is intended

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		• "PSC may lead to advanced cirrhosis" This may understate how common cirrhosis and advanced liver disease are in PSC. In an observational series of 174 patients with PSC who underwent a liver biopsy, advanced fibrosis or cirrhosis was found in 43% of patients with asymptomatic disease, and in 69% of those who were symptomatic [1]. In a retrospective cohort study using UK data, cirrhosis, portal hypertension, and liver failure occurred in 18.6, 14.5, and 8.8 per 1,000 person-years, respectively, among patients with PSC [2]. • "There are currently no licensed treatments for PSC" We recommend noting that, despite clinical trials over several decades and with nearly 20 different pharmacotherapies, no established medical treatment is available which has been shown to prolong survival or reduce the need for liver transplantation in patients with PSC [3-5]. • "Evidence for UDCA's impact on long-term outcomes is uncertain" To better reflect current understanding of UDCA's impact on PSC, we suggest clarifying that UDCA has not been shown to meaningfully modify long-term progression of PSC [6], and that higher doses (28–30 mg/kg/day) have been associated with increased rates of serious clinical endpoints, including death, transplantation, and complications [7]. • "In people with extreme cirrhosis, a liver transplant may be required" With liver transplantation being the only life-extending treatment option for patients with PSC, the disease is among the leading indications for liver transplantation in the UK, accounting for 12% of liver transplants in	to be a brief overview of the disease area. The following changes have been made to the background: • "PSC may lead to advanced cirrhosis" has been updated to "PSC often leads to advanced cirrhosis" • "[PSC] is most often diagnosed between the ages of 30 and 40" has been updated to "[PSC] is most often diagnosed between the ages of 30 and 40, but can occur at any age"

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		2024/2025 [8]. Early referral for transplant assessment is recommended in patients with cirrhosis and/or portal hypertension with complications, or when UKELD or MELD scores rise towards the minimum listing thresholds [1]. It is estimated that almost 30–40% of individuals with PSC will receive liver transplantation in their lifetime [9, 10]. However, the disease recurs in approximately one-third of liver transplant recipients, leading to graft loss and need for re-transplantation [11]. Furthermore, around one-third of patients with PSC and pre-existing IBD experience worsening disease following transplantation [12]. We suggest that the text is updated to more precisely reflect this. • "PSC can also cause cholangiocarcinoma, a cancer of the bile ducts, which is the leading cause of deaths due to PSC" The impact of PSC on cancer-related morbidity and mortality should be outlined in greater detail. Mortality is 3–4 fold higher in patients with PSC compared with age, sex and practice-matched general population controls [2,13], with the mean time from diagnosis to death or liver transplantation 10–22 years [1]. Patients are more likely to develop cancers of the bile ducts, gallbladder, liver, and colon, including cholangiocarcinoma, gallbladder cancer, and colorectal cancer. Overall, the life-time risk for hepatobiliary cancers is 7-15% [14]. This cancer and mortality risk, together with ongoing surveillance, may also increase psychological burden through anxiety about malignancy, procedures and uncertainty in a disease with no treatment to halt progression [15,16]. • "The cause of PSC is unknown, but current research suggests that the disease may be triggered by an unknown bacteria or virus in people who are genetically predisposed to it."	• "The bile ducts of people with PSC can become infected, which can lead to sepsis if untreated" has been added

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		While the pathogenesis of PSC is still poorly understood, it likely involves interactions between cholangiocytes, immune cells, and cells that maintain the extracellular matrix, with bile constituents and factors related to the gut microbiota and gut inflammation also likely involved [17]. • "PSC is most often diagnosed between the ages of 30 and 40." Some UK real-world data suggest that PSC may be diagnosed at an older age in routine practice; therefore, we suggest updating this to 30 to 50 years [2,19] References 1. Chapman, M. H., D. Thorburn, G. M. Hirschfield, G. G. J. Webster, S. M. Rushbrook, G. Alexander, J. Collier, J. K. Dyson, D. E. Jones, I. Patanwala, C. Thain, M. Walmsley, and S. P. Pereira. 2019. 'British Society of Gastroenterology and UK-PSC guidelines for the diagnosis and management of primary sclerosing cholangitis', Gut, 68: 1356-78. 2. Liang, H., S. Manne, J. Shick, T. Lissoos, and P. Dolin. 2017. 'Incidence, prevalence, and natural history of primary sclerosing cholangitis in the United Kingdom', Medicine (Baltimore), 96: e7116. 3. EASL Clinical Practice Guidelines on sclerosing cholangitis. Journal of Hepatology, 2022; 77, 761-806 4. Bowlus, C. L., L. Arrive, A. Bergquist, M. Deneau, L. Forman, S. I. Ilyas, K. E. Lunsford, M. Martinez, G. Sapisochin, R. Shroff, J. H. Tabibian, and D. N. Assis. 2023. 'AASLD practice guidance on primary sclerosing cholangitis and cholangiocarcinoma', Hepatology, 77: 659-702 5. Krones E, Graziadei I, Trauner M, Fickert P. Evolving concepts in primary sclerosing cholangitis. Liver Int. 2012 Mar;32(3):352-69. doi: 10.1111/j.1478-3231.2011.02607.x. Epub 2011 Aug 17. PMID: 22097926	

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		6. Triantos, C. K., N. M. Koukias, V. N. Nikolopoulou, and A. K. Burroughs. 2011. 'Meta-analysis: ursodeoxycholic acid for primary sclerosing cholangitis', Aliment Pharmacol Ther, 34: 901-10. 7. Lindor, K. D., K. V. Kowdley, V. A. Luketic, M. E. Harrison, T. McCashland, A. S. Befeler, D. Harnois, R. Jorgensen, J. Petz, J. Keach, J. Mooney, C. Sargeant, J. Braaten, T. Bernard, D. King, E. Miceli, J. Schmoll, T. Hoskin, P. Thapa, and F. Enders. 2009. 'High-dose ursodeoxycholic acid for the treatment of primary sclerosing cholangitis', Hepatology, 50: 808-14. 8. NHS Blood and Transplant. Annual report on liver transplantation: report for 2024/2025 (1 April 2015–31 March 2025). Published August 2025. 9. Saner, F. H., A. Frey, B. O. Stuben, D. P. Hoyer, K. Willuweit, M. Daniel, J. Rashidi-Alavieh, J. W. Treckmann, and H. H. Schmidt. 2023. 'Transplantation for Primary Sclerosing Cholangitis: Outcomes and Recurrence', J Clin Med, 12. 10. Goode, E. C., A. B. Clark, G. F. Mells, B. Srivastava, K. Spiess, W. T. H. Gelson, P. J. Trivedi, K. D. Lynch, E. Castren, M. N. Vesterhus, T. H. Karlsen, S. G. Ji, C. A. Anderson, D. Thorburn, M. Hudson, M. A. Heneghan, M. A. Aldersley, A. Bathgate, R. N. Sandford, G. J. Alexander, R. W. Chapman, M. Walmsley, Uk-Psc Consortium, G. M. Hirschfield, and S. M. Rushbrook. 2019. 'Factors Associated With Outcomes of Patients With Primary Sclerosing Cholangitis and Development and Validation of a Risk Scoring System', Hepatology, 69: 2120-35. 11. Carbone, M., A. Della Penna, C. Mazzarelli, E. De Martin, C. Villard, A. Bergquist, P. D. Line, J. M. Neuberger, S. Al-Shakhshir, P. J. Trivedi, U. Baumann, L. Cristoferi, J. Hov, B. Fischler, N. H. Hadzic, D. Debray, L. D'Antiga, N. Selzner, L. S. Belli, and S. Nadalin. 2023. 'Liver Transplantation for Primary Sclerosing Cholangitis (PSC) With or Without Inflammatory Bowel Disease (IBD)-A European Society of Organ Transplantation (ESOT) Consensus Statement', Transpl Int, 36: 11729.	

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		12. Singh S, Loftus EV Jr, Talwalkar JA. Inflammatory bowel disease after liver transplantation for primary sclerosing cholangitis. American Journal of Gastroenterology. 2013;108(9):1417-1425. doi:10.1038/ajg.2013.163. 13. Aune, D., A. Sen, T. Norat, E. Riboli, and T. Folseraas. 2021. 'Primary sclerosing cholangitis and the risk of cancer, cardiovascular disease, and all-cause mortality: a systematic review and meta-analysis of cohort studies', Sci Rep, 11: 10646. 14. van Munster K, Bergquist A, Ponsioen C; Inflammatory bowel disease and primary sclerosing cholangitis: One disease or two? Journal of Hepatology, 2023; 80, 155-168 15. Ranieri, V., E. Kennedy, M. Walmsley, D. Thorburn, and K. McKay. 2020. 'The Primary Sclerosing Cholangitis (PSC) Wellbeing Study: Understanding psychological distress in those living with PSC and those who support them', PLoS One, 15: e0234624. 16. Loesken C, Maehder K, Buck L, Hartl J, Löwe B, Schramm C, Toussaint A. Understanding illness experiences of patients with primary sclerosing cholangitis: a qualitative analysis within the SOMA.LIV study. BMC Gastroenterol. 2023 Jan 13;23(1):12. doi: 10.1186/s12876-023-02645-2. PMID: 36635643; PMCID: PMC9838018 17. von Seth E, Karlsen TH, Tanaka A, Ponsioen C, Bergquist A. Primary sclerosing cholangitis. Lancet. 2026 Mar 20:S0140-6736(25)02582-6. doi: 10.1016/S0140-6736(25)02582-6. Epub ahead of print. PMID: 41871593. 18. Fatourou E, Hyde S, Hyde S, et al OWE-4 National audit of diagnosis, management and surveillance in primary sclerosing cholangitis in the United KingdomGut 2021;70:A9.	
	Genetic Alliance UK	Based on conversation with our member organisation, PSC Support, we suggest that this section would benefit from better emphasising the data available on the significance of symptoms like fatigue and pruritus (itching), which can be debilitating for people living with PSC. The high lifetime risk of	Thank you for your comment. The background is intended to be a brief overview of

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		aggressive cancers like gallbladder, liver and pancreatic cancers could also more clearly be stated in addition to cholangiocarcinoma. This is particularly given the challenges in early detection where symptoms may overlap with PSC itself. Additionally, it may be helpful to clarify that PSC can present at any age, including in children, and that a significant proportion of people (approx. 80%) also live with inflammatory bowel disease, which is associated with poorer outcomes. Further, we noted that the risk and burden of recurrent cholangitis, which can lead to hospitalisation and sepsis, also appears slightly understated. We understand this recent review published in the Lancet by Seth et al. 2026 is a particularly strong overview of current symptoms and clinical management of PSC, which is recognised to reflect well the patient experience of PSC in the UK: Primary sclerosing cholangitis - The Lancet 10.1016/S0140-6736(25)02582-6 We also feel it would be helpful to signpost a number of other peer-review publications that may support the NICE evaluation team in the next stage of the process is available on PSC Support's website here: https://pscsupport.org.uk/references/#a1 https://pscsupport.org.uk/publication-history/	the disease area. The following changes have been made to the background: • "PSC may lead to advanced cirrhosis" has been updated to "PSC often leads to advanced cirrhosis" • "[PSC] is most often diagnosed between the ages of 30 and 40" has been updated to "[PSC] is most often diagnosed between the ages of 30 and 40, but can occur at any age"

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			• "The bile ducts of people with PSC can become infected, which can lead to sepsis if untreated" has been added
	PSC Support	The background text notes that PSVC is most frequently diagnosed between the ages of 30 and 40. Incidence is highest around age 40 years, but it should be stressed that PSC occurs at any age, including in childhood. Cholangiocarcinoma (CCA) is a major risk for people with PSC. However, the scope omits the fact that up to 50% of CCA cases are diagnosed within the first year of a PSC diagnosis. This underscores the urgency of early therapeutic intervention. Furthermore, CCA mimics PSC and it is challenging to detect, mostly being detected too late for effective treatment. PSC patients live with the knowledge that they have a lifetime risk for CCA and other aggressive cancers including gallbladder carcinoma, hepatocellular carcinoma (HCC), and pancreatic cancer. The scope correctly mentions that PSC is often associated with IBD. We would like to emphasise that up to 80% of people with PSC also have IBD, and having both confers an even greater risk of colorectal cancer than those with IBD alone. People with PSC-IBD have to undergo an annual colonoscopy (an invasive procedure), and have worse outcomes overall than PSC patients without PSC-IBD.	Thank you for your comment. The background is intended to be a brief overview of the disease area. The following changes have been made to the background: • "PSC may lead to advanced cirrhosis" has been updated to "PSC often leads to advanced cirrhosis" • "[PSC] is most often diagnosed

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		The scope doesn't mention one of the complications of PSC called acute cholangitis. This is an infection of the bile ducts, and occurs at any stage of the disease without warning. It doesn't present like a standard infection and clinicians unfamiliar with PSC (e.g. in A&E) often fail to identify and treat it. Untreated, cholangitis can lead to life-threatening sepsis and unplanned hospitalisation. Some people with PSC get recurrent acute cholangitis requiring rotating antibiotics. Recurrent cholangitis is an indication for liver transplant in the UK. Acute cholangitis is an important aspect of PSC that should be considered in this evaluation. While fatigue is correctly listed, we would like to emphasise that it is consistently the most commonly reported and debilitating symptom (75% patients report having fatigue) of PSC. Fatigue is experienced at all stages of the disease course, including post-transplant, and severely impacts HRQoL, regardless of liver blood test results and stage of disease. Pruritus too should be emphasised as a major debilitating symptom that is challenging to effectively treat, so much so that it can be an indication for liver transplant in its own right in the UK if cholestatic pruritic medications are not effective. The scope correctly identifies that there is no licensed therapy for PSC and notes that ursodeoxycholic acid (UDCA) is widely used. Our surveys show that around half of people with PSC in the UK are prescribed low to moderate doses of UDCA. It is not considered a treatment by patients and is taken in the absence of anything else, 'just in case' it helps. Transplant rates for PSC have increased not decreased over the last decades, strongly suggesting that it doesn't affect the disease course. The scope correctly states that UDCA is explicitly not recommended in the latest UK PSC Clinical Practice Guidelines. As mentioned above, in the UK, recurrent cholangitis and refractory pruritus are indications for liver transplant, in addition to cirrhosis. Transplant requires	between the ages of 30 and 40" has been updated to "[PSC] is most often diagnosed between the ages of 30 and 40, but can occur at any age" • "The bile ducts of people with PSC can become infected, which can lead to sepsis if untreated" has been added

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		lifelong immunosuppression in patients who are already at high risk for cancers. It should be noted that PSC returns (rPSC) in up to a third of patients who are transplanted.	
Population	Dr. Falk (company)	To reflect the expected wording of the marketing authorisation, the population should be defined as [redacted]	Thank you for your comment. Population is kept broad at the scoping stage. The population considered in NICE appraisals will usually be covered by the company's marketing authorisation.
	Genetic Alliance UK	We understand from PSC Support that it may be helpful for the committee to consider the heterogeneity of PSC, including those who are asymptomatic but remain at significant risk of disease progression and cancer, but defer to their expertise to elaborate on this point further.	Thank you for your comment. Population is kept broad at the scoping stage. The population considered in NICE appraisals will usually be covered by the company's marketing authorisation.
	PSC Support	The population is defined appropriately but we believe is missing young people, recurrent PSC (rPSC) and those with AIH overlap.	Thank you for your comment. Population is kept broad at the scoping stage. The population considered in NICE appraisals will usually be covered by

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			the company's marketing authorisation.
Subgroups	Dr. Falk (company)	Subgroups should be limited to those that are clinically relevant and compatible with the expected marketing authorisation. Small duct PSC subgroup should not be considered in the assessment as it is not represented in the anticipated licence or pivotal evidence base. Both IBD status and cirrhosis status were pre-specified subgroups in NUC-5, and these subgroups will be included within the submission. Subgroup results from NUC-5 suggest that NCA is superior to placebo regardless of IBD status or cirrhosis status. We would also like to note that the British Society of Gastroenterology (BSG) and UK-PSC guidelines suggest that PSC activity correlates only weakly, if at all, with IBD, and therefore the IBD status has limited prognostic significance in PSC [1]. References: 1. Chapman, M. H., D. Thorburn, G. M. Hirschfield, G. G. J. Webster, S. M. Rushbrook, G. Alexander, J. Collier, J. K. Dyson, D. E. Jones, I. Patanwala, C. Thain, M. Walmsley, and S. P. Pereira. 2019. 'British Society of Gastroenterology and UK-PSC guidelines for the diagnosis and management of primary sclerosing cholangitis', Gut, 68: 1356-78	Thank you for your comments. Population and subgroups are kept broad at the scoping stage. Where evidence allows, relevant subgroups may be considered.
	Genetic Alliance UK	We've been informed that several subgroups may warrant specific consideration: (1) young people, particularly those aged 16-25 transitioning between paediatric and adult services, as well as children under 16, given differing disease presentation and care needs; (2) people post-liver transplant, including both those with recurrent PSC and those without recurrence; (3) people receiving immunosuppressive therapies; and (4) people with co-existing autoimmune hepatitis (AIH), which are estimated to	Thank you for your comment. People who have previously had liver transplants, and autoimmune hepatitis status have been added

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		be ~10% of the PSC population, many of which are often excluded from trials and may experience more complexity in their care pathway.	as subgroups. Where evidence allows, other relevant subgroups may also be considered.
	PSC Support	PSC can occur at any age, including in babies and children. We strongly recommend that the scope includes the children and the adolescent transition population (aged 16–18), or that flexibility is built in so that a separate application is not later required, which may further delay access to treatment for this important group. We recommend that the scope includes rPSC post-transplant. Given that rPSC occurs in up to a third of transplanted patients, excluding this cohort might ignore a driver of long-term NHS costs and patient morbidity. If necessary. we ask that that flexibility is built in so that a separate application process is not later required. We recommend the scope includes PSC-AIH overlap syndrome. This group represents a distinct clinical phenotype (often seen in children and young adults). We ask that this group is included because they are excluded from clinical trials and yet are an important group in the PSC population. If AIH cannot be considered at this stage, we ask that that flexibility is built in so that a separate application process is not later required. We strongly request that the scope explicitly includes asymptomatic patients. Evidence indicates that 40–50% of PSC patients are asymptomatic at diagnosis, yet they remain at high risk of silent disease progression, including fibrosis and biliary strictures. Excluding this group or delaying treatment until symptoms appear (e.g., pruritus) misses the window where norucholic acid may be most effective at slowing disease progression. The evaluation must consider the clinical benefit of preventing end-stage liver disease, rather than just managing existing symptoms.	Thank you for your comment. People who have previously had liver transplants, and autoimmune hepatitis status have been added as subgroups. Where evidence allows, other relevant subgroups may also be considered.

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Comparators	Dr. Falk (company)	We do not agree that endoscopic dilation is a suitable comparator for NCA and recommend that it is removed from the scope. The BSG and UK-PSC guidelines position endoscopic dilatation as a selective interventional procedure for the management of certain dominant biliary strictures in a specific subset of PSC patients, rather than as a routine treatment for PSC. The guideline also notes that the role of endoscopic therapy in PSC remains incompletely understood, and that patients should not ordinarily undergo endoscopic retrograde cholangiopancreatography (ERCP) unless expert multidisciplinary assessment has established a clear rationale for intervention. Newer studies have questioned the therapeutic relevance of endoscopic treatment of PSC, as even when endoscopic treatment of dominant strictures is safe, prognosis remains worse compared to those without dominant strictures [1,2]. Endoscopic dilation is therefore better considered not as standard of care but as part of complication management in selected patients, which is not disease modifying and would not be displaced by treatment with NCA. References: 1. Chapman, M. H., G. J. Webster, S. Bannoo, G. J. Johnson, J. Wittmann, and S. P. Pereira. 2012. 'Cholangiocarcinoma and dominant strictures in patients with primary sclerosing cholangitis: a 25-year single-centre experience', Eur J Gastroenterol Hepatol, 24: 1051-8. 2. Björnsson, Einar M.D., Ph.D.; Lindqvist-Ottosson, Joachim M.S.; Asztely, Mats M.D., Ph.D.1; Olsson, Rolf M.D., Ph.D.. Dominant Strictures in Patients with Primary Sclerosing Cholangitis. American Journal of Gastroenterology 99(3):p 502-508, March 2004.	Thank you for your comment. Identification of relevant comparators is inclusive at the scoping stage. The selection of relevant comparators will usually be guided by the established practice in the NHS during the appraisal. Companies and stakeholders are welcome to submit further evidence and information on the established practice in the NHS, and provide justification for excluding any comparators they believe are not relevant. The committee will consider which comparators are relevant during the appraisal based on the evidence submitted. Best supportive care has been added as a

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			comparator in light of the comments, with it noting that endoscopic dilation and liver transplant may be required in the natural course of the disease.
	Genetic Alliance UK	We understand that endoscopic dilation (ERCP) appears to be referenced as a comparator; however, we've been informed by PSC Support that ECRP is an invasive interventional procedure used selectively to relieve bile duct obstruction, rather than a disease-modifying treatment, and is therefore better characterised as part of complication management. Similarly, while ursodeoxycholic acid is used in practice, it is prescribed off-label in the UK and is not recommended in guidelines, with limited evidence of clinical benefit, and that current management for people living with PSC in the UK is instead largely supportive and focused on symptom control.	Thank you for your comment. Identification of relevant comparators is inclusive at the scoping stage. The selection of relevant comparators will usually be guided by the established practice in the NHS during the appraisal. Companies and stakeholders are welcome to submit further evidence and information on the established practice in the NHS, and provide justification for excluding any comparators they believe are not relevant. The committee will

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			consider which comparators are relevant during the appraisal based on the evidence submitted. Best supportive care has been added as a comparator in light of the comments, with it noting that endoscopic dilation and liver transplant may be required in the natural course of the disease.
	PSC Support	The comparators listed are ursodeoxycholic acid (UDCA) and endoscopic dilation. We estimate that around 50% of people with PSC in the UK are prescribed UDCA, despite there being no evidence that it improves long term outcomes. In fact, transplants for people with PSC have continued to rise over the last few decades, suggesting it doesn't improve long term outcomes. People take UDCA in the absence of any other treatment, in the hope that it might do something. In our experience, only a few people report that UDCA improves their lives. Most take it 'just in case' it does. For this reason, we do not consider UDCA to a comparator. Endoscopic dilation is an intervention for a subgroup of PSC patients with accessible strictures to relieve biliary obstruction and is not a treatment for	Thank you for your comment. Identification of relevant comparators is inclusive at the scoping stage. The selection of relevant comparators will usually be guided by the established practice in the NHS during the appraisal. Companies and stakeholders are welcome to submit further evidence and

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		PSC. It is carried out with ERCP, an invasive procedure that has a risk of pancreatitis. Therefore, we do not consider endoscopic dilation to be a comparator. For most people with PSC, standard of care is symptom management (where possible) and monitoring for cancers/ disease progression.	information on the established practice in the NHS, and provide justification for excluding any comparators they believe are not relevant. The committee will consider which comparators are relevant during the appraisal based on the evidence submitted. Best supportive care has been added as a comparator in light of the comments, with it noting that endoscopic dilation and liver transplant may be required in the natural course of the disease.
Outcomes	Dr. Falk (company)	We suggest adding liver fibrosis progression to the list of relevant outcomes. In PSC, fibrosis stage is a predictive marker of worse clinical prognosis, including earlier progression to liver transplantation or death [1-5]. No worsening of histological disease stage was also a component of the combined primary endpoint within the NUC-5 trial, which will be the primary evidence base for the appraisal. We therefore consider it relevant to the assessment of clinical effectiveness.	Thank you for your comment. Liver fibrosis has been added to the outcomes.

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		References 1. Wiesner, R. H., P. M. Grambsch, E. R. Dickson, J. Ludwig, R. L. MacCarty, E. B. Hunter, T. R. Fleming, L. D. Fisher, S. J. Beaver, and N. F. LaRusso. 1989. 'Primary sclerosing cholangitis: natural history, prognostic factors and survival analysis', Hepatology, 10: 430-6. 2. Farrant, J. M., K. M. Hayllar, M. L. Wilkinson, J. Karani, B. C. Portmann, D. Westaby, and R. Williams. 1991. 'Natural history and prognostic variables in primary sclerosing cholangitis', Gastroenterology, 100: 1710-7. 3. Broome, U., R. Olsson, L. Loof, G. Bodemar, R. Hultcrantz, A. Danielsson, H. Prytz, H. Sandberg-Gertzen, S. Wallerstedt, and G. Lindberg. 1996. 'Natural history and prognostic factors in 305 Swedish patients with primary sclerosing cholangitis', Gut, 38: 610-5. 4. Corpechot, C., F. Gaouar, A. El Naggar, A. Kemgang, D. Wendum, R. Poupon, F. Carrat, and O. Chazouilleres. 2014. 'Baseline values and changes in liver stiffness measured by transient elastography are associated with severity of fibrosis and outcomes of patients with primary sclerosing cholangitis', Gastroenterology, 146: 970-9; quiz e15-6. 5. de Vries, E. M., J. Verheij, S. G. Hubscher, M. M. Leeflang, K. Boonstra, U. Beuers, and C. Y. Ponsioen. 2015. 'Applicability and prognostic value of histologic scoring systems in primary sclerosing cholangitis', J Hepatol, 63: 1212-9.	
	Genetic Alliance UK	Genetic Alliance UK frequently hears from its member organisations how generic HRQoL measures may often overlook, or are designed so they are unable to capture, the lived experience of people living with rare conditions, and we understand this is also the case for PSC. For example, emphasis on the burden on quality of life due to symptoms like fatigue and pruritus would be more clinically meaningful to people living with this rare condition. Further, in transplant-related outcomes, this may include surrogate markers of disease progression (e.g. ELF score and other fibrosis markers), and a reduction in	Thank you for your comment. Specific measures are not identified at the scoping stage. Liver fibrosis has been added to the outcomes. NICE

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		the number of unplanned hospital admissions associated with complications (e.g. acute cholangitis). For these reasons, we felt it may be useful to highlight to the committee that PSC-specific measures are currently under development and expected to be completed by mid-2027, and therefore relevant to the timeline for this review. https://pscsupport.org.uk/research-weve-funded/psc-quality-of-life-measure/ PSC Support also indicated their intention to submit patient survey data to capture the broader impact of PSC on daily life, education and employment, alongside registry data, including international datasets with UK participants (~180 individuals), to support the evidence base that informs this evaluation. https://pscsupport.org.uk/research-weve-funded/	welcomes submissions of patient survey data.
	PSC Support	For patients, there is a transformative benefit from delaying or stopping the need for liver transplant and from stopping further liver fibrosis. We would like to see the scope include surrogate markers of fibrosis progression (e.g., ELF score, transient elastography/FibroScan) as secondary outcomes. For asymptomatic patients, quality of life may remain stable in the short term, but the value of the norucholic acid lies in avoiding the future costs and QALY loss associated with complications, liver transplantation and cholangiocarcinoma. We propose that the scope includes the outcomes like unplanned hospital admissions, advanced liver disease complications (including portal hypertension, varices, jaundice and hepatic encephalopathy), incidence of acute cholangitis, and of hepatobiliary and colorectal cancers. From a patient perspective, current generic quality-of-life tools fail to capture the daily reality of PSC; therefore, we strongly recommend the inclusion of	Thank you for your comment. Specific measures are not identified at the scoping stage. Liver fibrosis, hospital admissions, and incidence of acute cholangitis and other complications have been added to the outcomes. Companies and stakeholders are welcome to submit any further evidence on the condition and/or the treatment effects of the technology on the

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		PSC-specific patient reported outcome measures and symptom assessment tools to ensure the Committee sees the full value of this treatment. The patient centric, PSC-specific UK-PSC quality of life measure is currently being developed and we hope will be available for use in 2027. We intend to submit evidence from a targeted PSC patient survey (to be launched Apr/May 2026). This survey will capture data on the hidden burden of PSC, including the impact of fatigue and pruritus on productivity, and the psychological burden of living with the possibility of cancer and/or liver transplant. We request that the Committee accepts this (and patient organisation registry data*) to provide a source of utility weights where trial data is insensitive, as we believe trial-based EQ-5D data may fail to reflect the episodic and fluctuating nature of PSC symptoms. Furthermore, our survey will provide evidence on carer burden. *The USA patient organisation, PSC Partners, has a global patient registry that includes data on 134 UK patients, which they are willing to share with us to submit as part of our evidence submission.	condition during the appraisal.
Equality	Dr. Falk (company)	As PSC is a rare disease, it is important that eligible patients have equitable access to new therapies irrespective of where they are treated. Access may otherwise vary because PSC care is concentrated in specialist centres and current management practices differ across the NHS. The lack of a defined referral pathway may further contribute to inequity in access to best practise and care, as current BSG/UK-PSC guidelines recommend referral for expert multidisciplinary assessment only in symptomatic, evolving or complex disease. PSC also disproportionately affects men compared with women.	Thank you for your comment. These issues have been added to the equalities impact assessment (EIA) form
	Genetic Alliance UK	There is a potential risk that certain groups living with PSC could be disadvantaged if not explicitly considered, including children and young	Thank you for your comment. These issues

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		people, and those with co-existing conditions such as AIH who may have been excluded from clinical trials. We therefore suggest that any consideration of how the evaluation may help mitigate this at the draft scoping stage.	have been added to the equalities impact assessment (EIA) form
	PSC Support	Age: PSC often begins in childhood we recommend including the 16–18 transition group to ensure equitable access as they enter adult NHS pathways. Invisible symptoms: we are also concerned about invisible disabilities. Our surveys tell us that around 75% of PSC patients suffer from debilitating exhaustion or brain fog, and about 22% have to miss work or school because of the intensity of the itching (pruritus). People with PSC are often diagnosed at a time when they are having families, or trying to progress their careers. We are concerned that EQ-5D could miss the impact of invisible symptoms and we risk undervaluing how much this drug actually improves a patient's life. Evidence: we recommend requesting the following: Supplemental patient survey data: we recommend looking at data from patient organisations (patient surveys) and international registries to help quantify the impact of PSC and aspects of PSC (things like brain fog, itch and fatigue) on productivity. Carer burden: PSC affects the whole household. We recommend looking at the impact on loved ones.	Thank you for your comment. These issues have been added to the equalities impact assessment (EIA) form
Other considerations		No comments	

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Questions for consultation	Dr. Falk (company)	Question: How is primary sclerosing cholangitis managed in the NHS? PSC management in the NHS is largely reactive and focused on monitoring, surveillance, and treatment of complications. In addition to the points outlined in responses above, PSC is associated with a high volume of non-elective hospital admissions, consistent with the burden of recurrent complications such as bacterial cholangitis, biliary strictures, and progressive liver disease. Its prolonged but highly variable disease course also makes it difficult to predict which patients will progress more rapidly. At the same time, there is no formalised referral pathway for PSC, and access to specialist centres depends on disease severity, symptom burden, and local expertise, adding further uncertainty for patients with PSC. Question: Is ursodeoxycholic acid used to treat primary sclerosing cholangitis in the NHS? Is it routinely used? UDCA use in the UK has been reported at 52% of patients with PSC [1], however the BSG and UK-PSC guidelines recommend against the routine use of UDCA in newly diagnosed PSC, rating this as a strong recommendation supported by good-quality evidence. Discussions with clinical experts within the field of PSC suggest that UDCA treatment initiation is driven more by individual centre practice and patient preference than by clearly defined clinical characteristics, with prescribing occurring in a context of lack of alternative treatment options and reluctance to leave patients without any form of therapeutic intervention. Moreover, the evidence for UDCA in PSC remains limited; meta-analyses of published data have not demonstrated a clear effect on disease progression,	Thank you for your comment. BSC has been added to the list of comparators.

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		time to liver transplantation, or other patient-relevant outcomes [2,3]. Notably, higher-dose UDCA has been associated with adverse outcomes [4]. References 1. Fatourou E, Hyde S, Hyde S, et al OWE-4 National audit of diagnosis, management and surveillance in primary sclerosing cholangitis in the United KingdomGut 2021;70:A9. 2. Shi J, Li Z, Zeng X , et al. Ursodeoxycholic acid in primary sclerosing cholangitis: meta-analysis of randomized controlled trials. Hepatol Res 2009;39:865–73.doi:10.1111/j.1872-034X.2009.00527.x 3. Triantos, C. K., N. M. Koukias, V. N. Nikolopoulou, and A. K. Burroughs. 2011. 'Meta-analysis: ursodeoxycholic acid for primary sclerosing cholangitis', Aliment Pharmacol Ther, 34: 901-10. 4. Lindor KD , Kowdley KV , Luketic VA , et al . High-dose ursodeoxycholic acid for the treatment of primary sclerosing cholangitis. Hepatology 2009;50:808–14.doi:10.1002/hep.23082 Question: Where do you consider norucholic acid will fit into the existing care pathway for PSC? NCA is a treatment option for all PSC adult patients with large duct disease, regardless of prior or concomitant UDCA treatment. Question: Please select from the following, will norucholic acid be: a. Prescribed in primary care with routine follow-up in primary care	

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		b. Prescribed in secondary care with routine follow-up in primary care c. Prescribed in secondary care with routine follow-up in secondary care d. Other (please give details): We anticipate that NCA will fall into category C: Prescribed in secondary care with routine follow-up in secondary care. Question: Would norucholic acid be a candidate for managed access? Based on currently available data, Dr Falk expects NCA to be a cost-effective and suitable for routine commissioning. However, a managed access agreement may be considered to address any remaining uncertainty. Question: Do you consider that the use of norucholic acid can result in any potential substantial health-related benefits that are unlikely to be included in the QALY calculation? Please identify the nature of the data which you understand to be available to enable the committee to take account of these benefits. NCA is an oral, once-daily treatment, which does not require dose titration, offering a simple regimen that may improve patient adherence and reduce treatment burden. PSC also has a considerable impact on the lives of patients' families and caregivers, which may be difficult to capture within the QALY calculations [1]. There is also the value of hope associated with access to a licensed treatment. This is a factor that does not come into consideration in traditional health technology assessments (HTAs). However, an ISPOR taskforce found	The committee will consider evidence submitted regarding benefits that would not be captured by

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		that it has positive value, and although difficult to quantify, should be considered by HTA authorities [2]. Relevant evidence could include patient, clinician, and carer testimony. References: 1. Ranieri V, Kennedy E, Walmsley M, Thorburn D, McKay K. The Primary Sclerosing Cholangitis (PSC) Wellbeing Study: Understanding psychological distress in those living with PSC and those who support them. PLoS One. 2020 Jul 6;15(7):e0234624. doi: 10.1371/journal.pone.0234624. PMID: 32628685; PMCID: PMC7337345 2. Reed SD, Yang J-C, Gonzalez JM, Johnson FR. Quantifying Value of Hope. Value in Health. 2021;24(10):1511 - 1519. doi:https://doi.org/10.1016/j.jval.2021.04.1284	standard utility data as part of the appraisal.
	PSC Support	How is PSC managed in the NHS? What is considered standard care for it in current NHS practice? PSC requires lifelong follow-up in secondary or tertiary care. Even for asymptomatic patients, once PSC is diagnosed, patients are monitored for the following annually: ● Cancer risk (annual imaging, 6-monthly if there is cirrhosis) ● Osteoporosis assessment (bone density) ● Symptom assessment (such as itch, pain and fatigue) - alternative causes checked and treated where possible). ● Malabsorption of fat-soluble vitamins assessment (in the case of more advanced PSC) ● IBD screening (if IBD is present - annual colonoscopy)	Thank you for your comment. BSC has been added to the list of comparators.

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		● Liver and bile ducts (extent of damage assessment) ● Some patients are given UDCA ● Patients seen more frequently with more advanced/ complex disease. If it is not routinely used but is used in some cases, please describe the clinical characteristics of the patients in whom clinicians would consider ursodeoxycholic acid. The UK guidelines specifically do not recommend the use of ursodeoxycholic acid (UDCA). However, in our experience, PSC patients often report wanting to take something, even without evidence it will help, just in case it does help. This is a disease where patients have zero control over how the disease will progress or when. We suspect UDCA is prescribed to patients who want to take it, including those who were prescribed it before the change in guideline recommendation and those with elevated ALP. Where do you consider norucholic acid will fit into the existing care pathway for PSC? It is expected to be a first-line disease-modifying therapy to slow fibrosis and delay the need for transplant/ reduce risk of cancers. PSC patients routinely attend secondary or tertiary clinics. However, symptom medications and some IBD medications, are initially prescribed at consultant level, are then prescribed on repeat by GPs. The fact that many people with PSC are trying to hold down jobs and minimise time of work/ university, trips to hospitals for medications are minimised if at all possible.	
	Genetic Alliance UK	Given the complexity of this rare condition, and potential routes for consideration on the above points, Genetic Alliance UK would see considerable value in holding a workshop with the stakeholders listed to	Thank you for your comment. NICE decides whether to hold

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Additional comments on the draft scope		ensure some of these complexities described are adequately accounted for in the evaluation process.	a scoping workshop based on the level of uncertainty about the relevancy of the scope that a workshop could address. NICE made the decision not to hold a workshop because it believed uncertainties that would affect the scope would not be addressed, but there will be many opportunities for engagement throughout the appraisal process to address complex issues and uncertainties.
	PSC Support	There is currently no proven medical therapy to slow or stop disease progression. PSC progresses unpredictably at a non-linear rate, with some patients progressing to transplant within months to a year, and others for decades with slow liver fibrosis. There are no effective tools that doctors can use to provide an individual prognosis. Some people with PSC live with daily debilitating (and often invisible and unpredictable) symptoms. People with PSC are at a higher risk of aggressive cancers than the general population, and in particular, CCA, the leading cause of death in PSC, mimics PSC and is challenging to detect as there are no effective surveillance options. People with PSC live with this knowledge and have reported that one of the hardest aspects of PSC is the emotional impact of not knowing what is going to happen and when. We would welcome the opportunity to contribute to a	Thank you for your comment. The committee will consider the experience of people with PSC in its decision making. NICE decides whether to hold a scoping workshop based on the level of uncertainty about the relevancy of the scope that a workshop could

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		Workshop, should the Committee feel it is appropriate given the unpredictability and complexity of PSC and its impact on patients. We would like to suggest some additional information sources about PSC: • von Seth E, Karlsen TH, Tanaka A, Ponsioen C, Bergquist A. Primary sclerosing cholangitis. *The Lancet.* 2026 Mar 20. • Trivedi PJ, Bowlus CL, Yimam KK, Razavi H, Estes C. Epidemiology, natural history, and outcomes of primary sclerosing cholangitis: a systematic review of population-based studies. *Clinical Gastroenterology and Hepatology.* 2022 Aug 1;20(8):1687-700. • PSC and PSC care: https://pscsupport.org.uk/get-information/ • Patient insights on living with PSC: https://pscsupport.org.uk/surveys/insights-living-with-psc/	address. NICE made the decision not to hold a workshop because it believed uncertainties that would affect the scope would not be addressed, but there will be many opportunities for engagement throughout the appraisal process to address complex issues and uncertainties.

The following stakeholders indicated that they had no comments on the draft remit and/or the draft scope

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