National Institute for Health and Care Excellence

Highly Specialised Technologies

Odevixibat for progressive familial intrahepatic cholestasis ID1570

Please note: Comments received in the course of consultations carried out by NICE are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the submissions that NICE has received, and are not endorsed by NICE, its officers or advisory committees.

Comment 1: the draft remit

Section	Consultee/ Commentator	Comments [sic]	Action
Appropriateness	Albireo AB	Yes, it is appropriate for NICE to review this topic at this time. However, we believe the Single Technology Appraisal (STA) route is not appropriate and odevixibat should be appraised under the Highly Specialised Technologies (HST) route (please see "Additional comments on the draft scope" section below). PFIC is a very rare, seriously debilitating and life-limiting condition with no licensed pharmacological treatments, managed in just three highly specialist expert centres in England. Albireo believes that odevixibat will address a significant unmet medical need in the very small number of children with PFIC.	Thank you for your comment. The Topic selection oversight panel together with NHS England decide on the routing of technologies through the appraisal process. Following these discussions, it was agreed that this topic is appropriate for consideration as a highly specialised technologies (HST) evaluation.
	Neonatal and Paediatric	Yes. Whilst PFIC affects a small number of patients the consequences are severe in terms of quality of life and progressive liver failure. The pruritus	Thank you for your comment. No action needed.

Section	Consultee/ Commentator	Comments [sic]	Action
	Pharmacists Group (NPPG)	associated with PFIC is especially debilitating, resulting in a much worse quality of life compared to other paediatric liver conditions.	
	Children's Liver Disease Foundation	CLDF believe that this is a priority topic due to their being no alternative treatment for PFIC other than surgery and liver transplantation. Children can experience pruritus, slow growth, pancreatitis, thicker skin and hearing problems with this condition which impacts their quality of life and those of their family. Pruritus is a common symptom of PFIC and as well as severe itching, can cause fatigue, disturbed sleep, reduced appetite, nausea and vomiting.	Comment noted. NICE aims to provide draft guidance to the NHS within 6 months from the date when marketing authorisation for a technology is granted. NICE has scheduled this topic into its work programme. No action needed.
Wording	Albireo AB	Yes, the wording of the remit is correct.	Thank you for your comment. No action needed
	Neonatal and Paediatric Pharmacists Group (NPPG)	Yes.	Thank you for your comment. No action needed
	Children's Liver Disease Foundation	No comment.	No action needed.
Timing Issues	Albireo AB	Timely reimbursement of odevixibat is important and urgent because there are no licensed treatments for PFIC and the disease has significant negative impact on patient morbidity and mortality. If the technology is not evaluated in a timely manner this would lead to delays in treatment, resulting in poorer outcomes for children with substantial unmet need.	Comment noted. NICE aims to provide draft guidance to the NHS within 6 months from the date when marketing authorisation for a technology is

Section	Consultee/ Commentator	Comments [sic]	Action
			granted. NICE has scheduled this topic into its work programme. No action needed.
	Neonatal and Paediatric Pharmacists Group (NPPG)	When the clinical trials are complete, children who are thriving on treatment should have early access to ongoing therapy without risk of treatment cessation and return of significant symptoms.	Comment noted. NICE aims to provide draft guidance to the NHS within 6 months from the date when marketing authorisation for a technology is granted. NICE has scheduled this topic into its work programme. No action needed.
	Children's Liver Disease Foundation	High due to there currently being no alternative treatment other than surgery and liver transplantation. Current therapies only reduce symptoms. However please see comment below. *(Further comments noted in 'additional comments on the draft remit' section)*	Comment noted. NICE aims to provide draft guidance to the NHS within 6 months from the date when marketing authorisation for a technology is granted. NICE has scheduled this topic into its work programme. No action needed.
	British Association for the Study of the Liver (BASL)	There isn't any trial data yet, and we would have thought that we need that first to evaluate efficacy and SE profile (e.g. bile salt diarrhoea)? There are other IBAT inhibitors in development but we can see the point of appraising this one if it has taken the early lead.	Comment noted. NICE aims to provide draft guidance to the NHS within 6 months from the date when

Section	Consultee/ Commentator	Comments [sic]	Action
			marketing authorisation for a technology is granted. NICE has scheduled this topic into its work programme. No action needed
Additional comments on the draft remit	Albireo AB	The technology should be referred to as odevixibat; the name A 4250 is no longer used.	Comment noted. The scope has been updated.
	Children's Liver Disease Foundation	We believe that this therapy and any therapy for PFIC should be assessed through the NICE Highly Specialised Technology Appraisal. Specialist paediatric liver disease services for all children in the UK come under NHS England's Highly Specialised Commissioning Services and patients are seen in one of only three specialist paediatric liver centres in the UK (Birmingham Children's Hospital NHS Foundation Trust; King's College Hospital NHS Foundation Trust; Leeds Teaching Hospitals NHS Trust). https://www.england.nhs.uk/commissioning/wp-content/uploads/sites/12/2018/12/Highly-Specialised-Services-2018-v2.pdf All other NICE appraisals that CLDF have been involved with in the past have been through the highly specialised technology route. Paediatric liver conditions, including PFIC, are rare conditions and as a result many professionals will not have a full understanding due to the complex and rare nature of the conditions.	Thank you for comment. The Topic selection oversight panel together with NHS England decide on the routing of technologies through the appraisal process. This topic will be evaluated as a highly specialised technology.

Comment 2: the draft scope

Section	Consultee/ Commentator	Comments [sic]	Action
Background information	Albireo AB	The reference to approx. 32 children per year requiring genetic testing for PFIC does not give a reliable indication of the number of diagnosed cases (please see Q1 in "Questions for consultation" section below). The description of liver transplant as a 'definitive' treatment option is misleading: liver transplant is not necessarily curative for patients and second transplants are sometimes required.[1] The impact of itching/pruritus on patients, their caregivers and family extends well beyond "interrupting sleep and contributing to fatigue". It can completely disrupt every aspect of life. Parents have shared that their infants have scratched through their skin, causing deep wounds. Children and parents have described post-traumatic stress disorder due to both symptoms experienced that disrupt their quality of life, and also due to extended hospital stays, medical tests and treatments related to PFIC. Babies who experience insatiable pruritus can develop into children challenged by impulse control and other social-emotional disabilities. Adolescents with PFIC have described bullying and social isolation from classmates and teachers, and they feel ashamed about their uncontrolled itching. Of consequence is also the sleep disruption to all members of the family. This impacts growth and development of a child affected by PFIC, and their ability - as well as that of any siblings - to participate in school and other activities. Caregivers have described strained relationships, divorce, and having to make difficult trade-offs around their careers and managing a child with a serious, progressive chronic liver condition. In the draft scope, it is not clear that age at diagnosis is prognostic of outcomes and an indicator of disease severity, with earlier treatment resulting in improved survival outcomes.	Thank you for your comment. The background section is intended to provide a brief summary of the condition. More details on the disease and its complications will be discussed during the development of the appraisal. The background section was amended to indicate that liver transplant remains the only definitive treatment for some patients with PFIC.
	Neonatal and Paediatric Pharmacists Group (NPPG)	Other significant complications of PFIC are the fat soluble vitamin deficiencies caused by malabsorption, leading to visual disturbance, bone disease (rickets), neurological impairment and coagulopathy. Management of these requires high doses of oral or IM vitamins.	Thank you for your comment. The background section is intended to provide a brief summary of the

Section	Consultee/ Commentator	Comments [sic]	Action
		The severe pruritus can also affect development and educational attainment as well as interrupting sleep. The primary treatment for PFIC is nutritional support (including vitamins) and treatments for symptomatic control - primarily to abate the pruritus. For the latter, medical therapies include ursodeoxycholic acid, bile acid sequestrants (colestyramine), rifampicin, ondansetron and occasionally naltrexone. If medical therapy fails then surgical intervention is trialled with external or internal biliary diversion, or ultimately liver transplantation.	condition. More details on the disease, its complications and management will be discussed during the development of the appraisal. No action needed.
	Children's Liver Disease Foundation	Accurate.	No action needed
The technology/ intervention	Albireo AB	In people with PFIC, bile acids accumulate to toxic levels in the liver.[2] Jaundice, pruritus, and elevated bile acid levels in the liver and serum are primary characteristics of cholestatic liver diseases. In addition to causing progressive liver disease, excessive accumulation of bile acids can lead to problems with filtering blood, breaking down fats, absorbing vitamins and clotting blood.[3] The ileal bile acid transporter (IBAT) is primarily responsible for mediating the uptake of bile acids from the small intestine to the liver as part of a process known as enterohepatic circulation. Typically, approximately 95% of bile acids are recirculated via the IBAT to the liver.[4] Odevixibat inhibits the IBAT, leading to a reduction in bile acids returning to the liver and represents a promising approach to treating cholestatic liver diseases. Odevixibat has been shown to reduce serum bile acids in children with cholestatic pruritus (phase II study, 43-98% reduction) and was well tolerated in phase II with no treatment-emergent serious adverse events. Odevixibat has orphan designation with PRIME status.	Thank you for your comment. The committee will consider the clinical evidence during the development of the appraisal. No action needed.
	Neonatal and Paediatric	Yes. Important to note that it prevents toxic levels of bile acids within the liver thus reducing the risk of cirrhosis and hepatocellular carcinoma. It also	Thank you for your comment. The

Section	Consultee/ Commentator	Comments [sic]	Action
	Pharmacists Group (NPPG)	reduces systemic bile acid load which has the potential to significantly improve pruritus.	committee will consider the clinical evidence during the development of the appraisal. No action needed.
	Children's Liver Disease Foundation	Yes.	No action needed.
Population	Albireo AB	Odevixibat is expected to be suitable for all patients with PFIC (except those with BSEP3 mutations). In the UK, this is estimated to be around 300-350 patients in total, with incidence of 8-12 patients per year. All types of PFIC exist worldwide and both sexes seem to be equally affected.[5] All PFIC types have a common underlying pathogenesis, i.e., disruption of bile formation and bile transport through the liver.[2] Odevixibat's phase III programme includes a randomised, double-blind, placebo-controlled clinical trial (PEDFIC 1) in patients ages 6 months to 18 years with PFIC subtypes 1 or 2, and an open-label extension trial (PEDFIC 2) to assess long-term safety and durability of response, with a second cohort in PEDFIC 2 that has enrolled PFIC patients of all ages and PFIC types.	Thank you for your comment. No action needed.
	Neonatal and Paediatric Pharmacists Group (NPPG)	**Children** and adults This is primarily a paediatric liver disease and it should be considered in this population ahead of or with adults. Children have usually undergone liver transplant or died before reaching adulthood, although type 3 can present later.	Thank you for your comment. The population is currently broad to include children and adults. Any recommendation will depend on the marketing authorisation. No action needed.

Section	Consultee/ Commentator	Comments [sic]	Action
	Children's Liver Disease Foundation	Yes – however there are three types of PFIC currently identified which may be worth noting: FIC1 deficiency (PFIC 1) BSEP deficiency (PFIC 2) MDR3 deficiency (PFIC 3) – while PFIC 1 and 2 tend to occur in infancy, PFIC 3 can occur during infancy, childhood and even into young adulthood. Pruritus tends to be milder in this group but higher risk of other complications and there is a much wider range of severity.	Thank you for your comment. The population is currently broad and will depend on the final marketing authorisation. No action needed.
	British Association for the Study of the Liver (BASL)	We don't have a feel for the very early onset of more severe forms PFIC1 and PFIC2 therefore not sure how easily any drug would stave off transplantation there. PFIC3 may be more promising as a more gradual disease.	Thank you for your comment. The population is currently broad and will depend on the final marketing authorisation. No action needed.
Comparators	Albireo AB	These are the standard treatments currently used for PFIC in the NHS. However, it should be clarified that there is no defined pharmacological standard of care for PFIC and there are no licensed treatments.[6] The therapeutic choices are restricted to non-specific treatment of the symptoms and signs of the disease such as nutritional support, preventing vitamin deficiencies, and treatment of extrahepatic features.[7] Medical treatment options include off-label use of ursodeoxycholic acid (UDCA), rifampicin, antihistamines, naltrexone and cholestyramine. A minority of patients respond to these medications and, if so, only transiently. Most patients require surgical interventions such as partial external biliary diversion (PEBD) and/or liver transplantation.[8] Therefore, the current alternative care is PEBD or liver transplantation.[6] However, clinician feedback indicates that these are options of last resort, which is why so many off-label medications are given in the early stages after diagnosis.	Thank you for your comment. The appraisal committee will discuss the most appropriate comparator during the development of this appraisal. This will depend on the final marketing authorisation, the current treatment pathway, clinical and cost effectiveness evidence and current clinical practice. If comparators in the

Section	Consultee/ Commentator	Comments [sic]	Action
			submission differ from the scope, justification should be provided. No action needed.
	Neonatal and Paediatric Pharmacists Group (NPPG)	Yes, although I would add that multiple anti-pruritic agents are usually required at achieve any symptom relief so would include bile acid sequestrants, rifampicin, ondansetron, topical emollients	Thank you for your comment. The list of comparators has been kept broad and is not exclusive. The appraisal committee will discuss the most appropriate comparator during the development of this appraisal. If comparators in the submission differ from the scope, justification should be provided. No action needed.
	Children's Liver Disease Foundation	Yes	No action needed.
	British Association for the Study of the Liver (BASL)	IBAT inhibition in theory looks good for PFIC and would probably be first line if it worked as the other treatments either don't work or are surgical (biliary diversion).	Thank you for your comment. No action needed.
Outcomes	Albireo AB	The NAPPED study, the world's largest PFIC natural history database, suggests that reduction of bile acids is associated with improvements in native liver survival.[9, 10]	Thank you for your comment. No action needed.

Section	Consultee/ Commentator	Comments [sic]	Action
		In Europe, the primary endpoint in our pivotal phase III trial is serum bile acid reduction. Our phase III programme includes subjects in the long-term extension trial, PEDFIC 2, some of whom have been on therapy for well over a year, and we will assess the number of patients requiring biliary diversion surgery and liver transplants. Disease progression and disease modification will be evaluated in terms of sBA levels and severity of pruritus, effect on growth and sleep, as well as measures of longer term progression like fibrosis and need for surgical intervention. HRQoL will be assessed using PedsQL inventory utilities mapped to the CHU-9D from the phase III study. Safety will be assessed by TEAEs, SAEs, hepatic events, hepatic laboratory parameters, INR, adverse events of interest, other clinical safety laboratory parameters and vital signs.	
	Neonatal and Paediatric Pharmacists Group (NPPG)	Yes	No action needed.
	Children's Liver Disease Foundation	All - but health-related quality of life (for patients and carers) benefit would in our opinion be greatest.	Thank you for your comment. No action needed.
Economic analysis	Albireo AB	The economic analysis described is appropriate and will be in line with the NICE reference case. We propose a cost-utility analysis across a lifetime horizon to capture the incremental costs and QALYs accrued over patients' lives.	Thank you for your comment. No action needed.
	Neonatal and Paediatric Pharmacists Group (NPPG)	Nil	No action needed.

Section	Consultee/ Commentator	Comments [sic]	Action
	Children's Liver Disease Foundation	No comment	No action needed
Equality and Diversity	Albireo AB	Assuming that NICE proceeds to scoping on the basis that odevixibat will be available to all suitable PFIC patients, we do not consider that the proposed remit and scope will need to be amended in order to meet NICE's equality aims. However, by appraising odevixibat under the STA route rather than HST, NICE is setting up a process that odevixibat will inevitably fail for cost per QALY reasons. The HST route was specifically designed for medicines for very rare conditions, enabling a higher cost per QALY threshold, a broader range of decision-making criteria and a faster timescale, recognising the particular challenges associated with developing treatments for these conditions. As such, the proposed appraisal method via STA risks having an adverse impact on people with extremely poor prognosis and quality of life, and their caregivers. This will prevent access to odevixibat by children who may progress to liver transplant and early death. There is a significant equality/equity issue with regard to lack of access to treatments for rare and ultra-rare diseases, which has been described extensively.[11] The EU and US orphan drugs acts were established to incentivise companies to research and develop treatments for rare and ultra-rare diseases. However, access to these therapies has not followed the regulatory trend, creating significant inequity and distress for patients and their caregivers. The Scottish Medicines Consortium (SMC) has already validated odevixibat as an ultra-orphan therapy, meaning that it will be appraised under its Ultra-orphan Pathway. It would be inconsistent for NICE to adopt a different route,	Thank you for your comment. No action needed. The Topic selection oversight panel together with the NHS decide on the routing of technologies through the appraisal process. This topic will be appraised as a highly specialised technology.

Section	Consultee/ Commentator	Comments [sic]	Action
		and could result in patients in Scotland having access to odevixibat well before those in England, Wales and Northern Ireland.	
	Neonatal and Paediatric Pharmacists Group (NPPG)	None identified	No action needed.
	Children's Liver Disease Foundation	No comment	No action needed.
Other considerations	Albireo AB	A lack of long-term outcomes available for patients with PFIC is a key limitation to evaluation of the clinical and cost-effectiveness of odevixibat, notably: • Survival • Treatment efficacy and durability: particularly PEBD, as some patients require a reversal of their diversion	Thank you for your comment. Long-term outcomes will be discussed during the appraisal. No action needed.
	Neonatal and Paediatric Pharmacists Group (NPPG)	This drug is being licensed as oral capsules but for use in children. There is no liquid formulation available.	Thank you for your comment. No action needed.
	Children's Liver Disease Foundation	No comment	No action needed.
Innovation	Albireo AB	Odevixibat is a novel bile acid modulator which is expected to be the first licensed pharmacological treatment for PFIC using pivotal phase III data to show reduction in serum bile acids, the underlying cause of the disease. It is likely to be the first IBAT inhibitor approved globally. Odevixibat is a once-daily oral medication, delivered in a capsule which can be opened and emptied into food for younger children.	Comment noted. The innovative nature of the technology will be considered throughout the course of the appraisal.

Section	Consultee/ Commentator	Comments [sic]	Action
		Odevixibat is a potent and selective inhibitor of the ileal bile acid transporter (IBAT), sometimes referred to as the apical sodium dependent bile acid transporter (ASBT), that has minimal systemic exposure at therapeutic doses and acts locally in the gut. There are currently no effective or approved pharmacological treatments for PFIC (standard medical treatments are supportive only). Therefore, new, non-invasive options like odevixibat represent a step-change in management of the condition because existing treatments have significant risk of treatment failure and disease recurrence, and can be extremely invasive. External biliary diversion is one approach to reducing pathologic bile acid accumulation in the body by diverting bile acids to an external stoma.[3] It involves the use of stoma, drainage bags, and nasogastric tubing, which presents a difficult choice for the parents of the children. Internal biliary diversions have also been performed and while initial results from these techniques have been promising, longer follow-up data are needed.[11] Liver transplantation is typically viewed as an option when patients have failed medical treatment and/or biliary diversion and have a poor quality of life (QoL) due to refractory pruritus, impaired growth, and/or irreversible fibrosis, cirrhosis and end-stage liver disease. However, liver transplantation is a complicated surgery with a 10-20% mortality rate; it is associated with significant risks, including infection and rejection and the need for lifelong anti-rejection medication, and is not always curative.[1, 12] In addition, there is a shortage of suitable organ donors. Survival in patients with PFIC not undergoing surgical diversion or liver transplant is 50% at the age of 10 and almost none at the age of 20 years, highlighting the rate of progression and the life-threatening nature of the disease.[1] Albireo is undertaking a multi-country study, including the UK, on Burden of Illness of PFIC with specific focus on caregiver burden; the results of this	

Section	Consultee/ Commentator	Comments [sic]	Action
		study will be available in early 2021. While the company's submission to NICE will include these aspects, we anticipate some difficulties in fully capturing the impact on the lives of parents, siblings, the wider family, and friends. Albireo acknowledges that NICE's reference case is focused on QALYs for patients and caregivers, plus NHS and social care costs. However, PFIC has profound impacts beyond physical and mental health alone (as captured through EQ-5D) including but not limited to educational attainment, ability to work, ability to contribute to society, ability to make and keep friends, and so on. These broader impacts of the disease could be reduced with better control.	
	Neonatal and Paediatric Pharmacists Group (NPPG)	Yes - this treatment is a step change in the way cholestatic liver diseases are managed and expected outcomes are mitigated. Reducing the development of cirrhosis and HCC should have a beneficial impact on quality of life and reduced need for liver transplantation, however the data to support that outcome is not yet readily available	Comment noted. The innovative nature of the technology will be considered throughout the course of the appraisal.
	Children's Liver Disease Foundation	Currently the only therapies available, only reduce the effects and complications of the condition e.g. to reduce jaundice and/or itching. Treatments used are recommended by their specialist depending on the features and severity of the condition and its effects. Furthermore, surgery and transplantation, carries risk, have varying degrees of success and are not appropriate for all children. For this reason, we believe access to any therapy such as this can result in a number of significant health related benefits in the management of PFIC.	Comment noted. The innovative nature of the technology will be considered throughout the course of the appraisal.
Questions for consultation	Albireo AB	**1. What is the prevalence and incidence of PFIC in England?** As a very rare disease, there are limited epidemiological data on PFIC. Albireo's analysis of published data, informed by UK clinician input, indicates that UK prevalence of PFIC is 300-350 patients, with incidence of 8-12 patients per year. Of course, NICE's remit is for England so we would expect the UK figures to reduce *pro rata*.	Thank you for your comments. No action needed.

Section	Consultee/ Commentator	Comments [sic]	Action
		2. Which treatments are established clinical practice in the NHS for PFIC? There are no licensed pharmacological treatments for PFIC. Established clinical practice involves treatment with UDCA or other supportive therapy, followed by PEBD and/or liver transplant. **3. Is Odevixibat (A 4250) likely to be considered a first-line treatment option for PFIC or would it only be considered after other treatments have failed?** Odevixibat is positioned as a first-line treatment option with the intention of avoiding or delaying future surgical intervention and/or transplantation. **4. Do the comparators currently listed in the draft scope reflect the treatments that are already in use in the NHS that will potentially be displaced by the uptake of Odevixibat (A 4250)?** The pharmaceutical therapies listed in the draft scope are used off-label and only provide supportive care as a bridge to surgery or transplant. Their use may be reduced or obviated by the use of odevixibat but they may still be used to provide short-term supportive care alone or in addition to odevixibat. The surgical treatments listed will potentially be displaced by odevixibat because reduction in serum bile acid levels has been shown to increase native liver survival, thus delaying or removing the need for these invasive interventions.	

Section	Consultee/ Commentator	Comments [sic]	Action
		5. At what stage in the current pathway is liver transplant likely to be offered as a treatment for PFIC? Liver transplantation is typically viewed as an option when patients have failed supportive treatment and/or biliary diversion and have a poor quality of life due to refractory pruritus, impaired growth, and/or irreversible fibrosis, cirrhosis and end-stage liver disease. **6. Are the outcomes listed appropriate? Specifically,** • **is change in serum bile acid level a clinically meaningful outcome?** Yes. Serum bile acid levels are associated with native liver survival. Reduction of bile acid levels below 102 µmol/L, or a 75% reduction from pre-diversion values, was associated with significantly increased native liver survival.[9, 10, 14] • **is Odevixibat (A 4250) expected to have any clinical benefit in terms of the number of patients experiencing disease progression or requiring liver transplant?** Yes, use of odevixibat is expected to delay or halt disease progression and reduce or avoid the need for surgery and/or liver transplantation.[6, 14] • **is Odevixibat (A 4250) expected to have any positive or negative impact on growth?** Odevixibat is expected to have a positive impact on growth because improvement in growth may be potentially related to the disease modifications induced by IBAT inhibition. Possible explanations for this may be pruritus relief, improvement in sleep, and greater absorption of fats due to modified bile acid profile in the gut.[6]	

Section	Consultee/ Commentator	Comments [sic]	Action
		7. Are patients with type 3 PFIC, (that is, those with PFIC that is linked to ABCB4 gene mutations/variations) likely to be eligible for treatment with Odevixibat (A 4250)? Yes. PFIC1 and PFIC2 together represent approximately two-thirds of cases of PFIC, and PFIC3 one-third of cases.[16] All PFIC types have a common underlying pathogenesis, i.e. disruption of bile formation and bile transport through the liver.[17] Odevixibat aims to decrease intestinal bile acid absorption and thereby reduce the high concentrations of circulating bile acids associated with pruritus and liver damage/failure. It has been studied in PFIC 3 as well as PFIC 1 and 2; based on the MoA, odevixibat is expected to be appropriate for all three PFIC types. **8. Are there any subgroups of people in whom the technology is expected to provide greater clinical benefits or more value for money, or other groups that should be examined separately?** No, odevixibat is suitable for all PFIC types (except those with BSEP3 mutations). **9. NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that the proposed remit and scope may need changing in order to meet these aims. In particular, please tell us if the proposed remit and scope:** • **could exclude from full consideration any people protected by the equality legislation who fall within the patient population for which Odevixibat (A 4250) will be licensed;** • **could lead to recommendations that have a different impact on people protected by the equality legislation than on the wider**	

Section	Consultee/ Commentator	Comments [sic]	Action
		population, e.g. by making it more difficult in practice for a specific group to access the technology; • **could have any adverse impact on people with a particular disability or disabilities.** Please see response above under the section entitled “Equality”. **10. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how it might improve the way that current need is met (is this a ‘step-change’ in the management of the condition)?** Please see response above in the section entitled “Innovation”.	
	Neonatal and Paediatric Pharmacists Group (NPPG)	In the first instance I would expect Odevixibat to be second or third line medical treatment for pruritus for PFIC, before biliary diversion surgery. However its beneficial effects on reduction of bile acid load in the liver and prevention of cirrhosis and HCC would make it appropriate for any patient with high bile acid levels and deranged liver function tests as a means of preventing progression to liver transplantation. I would expect the comparators in the draft scope and the additional ones listed in the above sections to potentially be displaced by the uptake of Odevixibat, although in trials not all children were able to reduce or stop other antipruritic therapies. Liver transplant is the last treatment option for PFIC after medical therapy and biliary surgery have failed, or the child has developed HCC.	Thanks for your comments. No action needed.

Section	Consultee/ Commentator	Comments [sic]	Action
		A change in serum bile acids is clinically meaningful and a useful marker of efficacy. I would expect fewer children to progress to liver transplantation although that data is not yet available. In trials some children have shown an improvement in growth. Patients with PFIC type 3 are less likely to respond to this treatment modality and unlikely to be eligible.	
	Children's Liver Disease Foundation	As stated above: We believe that this therapy and any therapy for PFIC should be assessed through the NICE Highly Specialised Technology Appraisal. Specialist paediatric liver disease service comes under NHS England's Highly Specialised Commissioning Services and patients are seen in one of only three specialist paediatric liver centres in the UK (Birmingham Children's Hospital NHS Foundation Trust; King's College Hospital NHS Foundation Trust; Leeds Teaching Hospitals NHS Trust). https://www.england.nhs.uk/commissioning/wp-content/uploads/sites/12/2018/12/Highly-Specialised-Services-2018-v2.pdf All other NICE appraisals that CLDF have been involved with for children with liver disease in the past have been through the highly specialised technology route. Paediatric liver conditions, including PFIC, are rare conditions and as a result many professionals will not have a full understanding due to the complex and rare nature of the conditions. There is a very small pool of consultants working in this area nationally.	Thank you for your comment. The Topic selection oversight panel together with the NHS decide on the routing of technologies through the appraisal process. This topic will be appraised as a highly specialised technology.
Additional comments on the draft scope	Albireo AB	Albireo Comments for NICE's Recommended Review under STA vs. HST According to the HST checklist provided by NICE (21 July 2020), odevixibat is currently routed to Single Technology Appraisal (STA) because NICE feels that it may not fully meet Highly Specialised Technologies (HST) criteria 1, 2, 4 and 5. It is our belief that odevixibat fully meets all 7 criteria and that it should be appraised under the HST process rather than STA:	Thank you for your comments. The Topic selection oversight panel together with the NHS decide on the routing of technologies through the appraisal

Section	Consultee/ Commentator	Comments [sic]	Action
		• Under Regulation 7 of SI 2013/259, NICE has the power to make a technology appraisal recommendation in relation to a health technology, where directed to do so by the Secretary of State. • Under Regulation 8, NICE has a separate power to make highly specialised technology recommendations in relation to highly specialised health technology, where directed to do so by the Secretary of State. • Technology appraisal recommendations and highly specialised technology recommendations are both defined in Regulation 2 of SI 2013/259. Crucially, a highly specialised technology recommendation is defined by reference to the term highly specialised health technology, which is defined as "a health technology intended for use in the provision of services for rare and very rare conditions provided for in regulations made under section 3B(1)(d) of the 2006 Act". • Services for rare and very rare conditions are listed in Schedule 4 to SI 2012/2996, which is made under Regulation 11 of the same SI. Regulation 11 is made under section 3B(1)(d) of the 2006 Act. Schedule 4 includes "specialist paediatric liver disease service". • In circumstances where NICE has been given a specific power to make highly specialised technology recommendations in relation to specialist paediatric liver disease service, NICE cannot lawfully consider a treatment that will fall within those services under an entirely separate power (namely, the power to make technology appraisal recommendations), and any direction from the Secretary of State that NICE should do so would run counter to the Regulation. In any event, given the likely pricing of odevixibat as a treatment for a very rare disease with significant burden, and the standard NICE threshold of £30,000 for non-specialised treatments, it would be entirely irrational from a public law perspective for NICE to pursue a process that odevixibat would inevitably fail.	process. This topic will be appraised as a highly specialised technology.

Section	Consultee/ Commentator	Comments [sic]	Action
		Furthermore, it is clear that it would be unreasonable and/or illogical for NICE to appraise odevixibat under the STA process when, as explained below, odevixibat meets the prioritisation criteria for HST: **Criterion 1:** NICE states that the size of the target patient group is not clear and we agree that as a very rare disease, there are limited epidemiological data. However, Albireo's analysis of published data, informed by UK clinician input, indicates that UK prevalence of PFIC is 300-250 patients, with incidence of 8-12 patients per year. Of course, NICE's remit is for England so we expect the UK figures to reduce *pro rata*. This is comparable to or less than other therapies already approved under the HST process. NICE also states that odevixibat could potentially be delivered via existing specialist services (PSS) rather than a highly specialised service (HSS), because it is an oral medication and because there is an existing PSS covering children with acute and chronic liver disorders. We do not believe this is appropriate because there is already a Specialist Paediatric Liver Disease Service defined within HSS which covers PFIC among a group of closely related progressive paediatric liver diseases, due to the rarity and highly specialised nature of the condition. Regardless of the delivery mechanism of the therapy, diagnosis and treatment of PFIC in England is managed only in King's College Hospital NHS Foundation Trust, Birmingham Women's and Children's Hospital NHS Foundation Trust, and Leeds Teaching Hospitals NHS Trust.[18] These are also the only clinical trial sites for PFIC in the UK. PFIC is listed specifically on page 8 of the NHS England Standard Contract for Specialist Liver Disease (Children) (E03/S(HSS)/d), which also states: "All chronic liver diseases should be managed by highly specialised NHS England commissioned services.[19] Patients whose condition is benign and self-limiting may be managed entirely in primary or secondary care services, but require consultant input from a highly specialised paediatric hepatology NHS England commissioned unit in some form".	

Section	Consultee/ Commentator	Comments [sic]	Action
		According to the NHS England Standard Contract for Paediatric Medicine: Gastroenterology, Hepatology and Nutrition cited by NICE, there are around 20 specialist centres for PGHN in England, and prevalence of the diseases covered generally ranges from 1:100 to 1:1,000.[20] According to the Contract, "Conditions such as abnormal Liver Function Tests (LFTs) related to obesity (not persistent, progressive), abnormal LFT's related to intestinal failure (not persistent, progressive, complex), abnormal LFT's related to IBD (not persistent, progressive or antibody positive), abnormal LFT's related to cystic fibrosis (not persistent, progressive) may be managed by a specialist paediatric gastroenterology unit in the first instance." Very rare, complex, genetic progressive diseases such as PFIC are not included in this definition. In addition, NICE's judgement that oral delivery of the medicine means a highly specialised service is not required seems perverse in that Albireo is being penalised for developing a formulation that minimises NHS costs and the time required of patients, and maximises convenience for patients and their families. This would appear to go against the spirit of developing new treatments and could discourage companies from developing the most convenient delivery formats for patients. **Criterion 2:** The target population group is clearly distinct because PFIC is diagnosed based on the presence of a genetic mutation. PFIC refers to a group of childhood cholestasis diseases with a common underlying pathogenesis, i.e. disruption of bile formation and bile transport through the liver.[17] Most recent publications on PFIC describe the types, each identified by unique gene mutations and clinical manifestations.[21]	

Section	Consultee/ Commentator	Comments [sic]	Action

Type	PFIC1	PFIC2	PFIC3	PFIC4	PFIC5	PFIC6
Gene (protein) Protein function	*ATP8B1* (FIC1) Phosphatidylserine flippase translocates phospholipids across the canalicular membrane	*ABCB11* (BSEP) ATP-dependent canalicular BA export pump	*ABCB4* (MDR3) Transports phosphatidyl-choline into canaliculi	*TJP2* (TJP2) Regulates passage of molecules between hepatocytes and prevents BA reflux	*NR1H4* (FXR) Nuclear BA receptor and regulates BA metabolism	*MYO5B* (Myosin 5b) Cell polarization and trafficking of BSEP
Phenotype (*all* with cholestasis and potential for cirrhosis)	• Diarrhea • Pancreatitis; insufficiency • Hearing loss • BRIC1 • ICP1	• Early-onset cirrhosis and HCC (first 5 years) • BRIC2 • ICP2	• Gallstones • Insidious onset • Higher rate of HCC, CCA	• Respiratory and neurological sequalae • Rapid progression • HCC risk	• Very rapid progression in infancy	• Episodic cholestasis • Microvillus inclusion disease in some
GGTP	Low/Normal	Low/Normal	High	Low or high[13]	Low/Normal	Low/Normal
Surgical therapies	• Biliary diversion • Liver transplant	• Biliary diversion • Liver transplant	Liver transplant	Liver transplant	Liver transplant	Liver transplant

Criterion 3: NICE agrees that this is fully met.

Criterion 4: NICE states that this is not met. This is strongly refuted by the evidence set out under Criterion 1.

Criterion 5: Odevixibat is expected to be priced to reflect the value it delivers, i.e. at a similar level to comparable orphan drugs in ultra-rare diseases with significant burden on patients, caregivers and the healthcare system and no licensed treatments, that have already been approved by NICE through the HST process. Therefore, Albireo considers that this criterion is fully met.

Criterion 6: NICE agrees that this is fully met.

Criterion 7: NICE agrees that this is fully met.

References

1. Pawlikowska L, Strautnieks S, Jankowska I, Czubkowski P, Emerick K, Antoniou A, et al. Differences in presentation and progression between severe FIC1 and BSEP deficiencies. Journal of hepatology. 2010;53(1):170-8.
2. Gunaydin M, Cil ATB. Progressive familial intrahepatic cholestasis: diagnosis, management, and treatment. Hepatic medicine: evidence and research. 2018;10:95.
3. Children's Liver Disease Foundation. Progressive familial intrahepatic cholestasis 2019 [Available from: https://childliverdisease.org/liver-information/childhood-liver-conditions/progressive-familial-intrahepatic-cholestasis/.

Section	Consultee/ Commentator	Comments [sic]	Action
		4. Graffner H, Gillberg PG, Rikner L, Marschall HU. The ileal bile acid transporter inhibitor A4250 decreases serum bile acids by interrupting the enterohepatic circulation. Alimentary pharmacology & therapeutics. 2016;43(2):303-10. 5. Srivastava A. Progressive familial intrahepatic cholestasis. Journal of clinical and experimental hepatology. 2014;4(1):25-36. 6. Kamath BM, Stein P, Houwen RH, Verkad HJ. Potential of ileal bile acid transporter inhibition as a therapeutic target in alagille syndrome and progressive familial intrahepatic cholestasis. Liver International. 2020. 7. European Association For The Study Of The Liver. EASL Clinical Practice Guidelines: management of cholestatic liver diseases. Journal of hepatology. 2009;51(2):237-67. 8. Ismail H, Kaliciński P, Markiewicz M, Jankowska I, Pawłowska J, Kluge P, et al. Treatment of progressive familial intrahepatic cholestasis: liver transplantation or partial external biliary diversion. Pediatric transplantation. 1999;3(3):219-24. 9. van Wessel DBE, Thompson RJ, Gonzales E, Jankowska I, Sokal E, Grammatikopoulos T, et al. Genotype correlates with the natural history of severe bile salt export pump deficiency. Journal of Hepatology. 2020. 10. Van Wessel D, Thompson R, Grammatikopoulos T, Kadaristiana A, Jankowska I, Lipinski P, et al. The natural course of FIC1 deficiency and BSEP deficiency: Initial results from the NAPPEDconsortium (NAtural course andprognosis of PFIC and effect of biliary diversion). Journal of Pediatric Gastroenterology and Nutrition. 2018;66(Supplement 2):650-2. 11. Shire. Equity and Access: Making the UK a rare disease leader 2017 [Available from: http://www.haeuk.org/wp-content/uploads/2015/07/Shire-Equity-and-Access-Making-the-UK-a-rare-disease-leader.pdf. 12. Mehl A, Bohorquez H, Serrano M-S, Galliano G, Reichman TW. Liver transplantation and the management of progressive familial intrahepatic cholestasis in children. World journal of transplantation. 2016;6(2):278. 13. Alissa FT, Jaffe R, Shneider BL. Update on progressive familial intrahepatic cholestasis. Journal of pediatric gastroenterology and nutrition. 2008;46(3):241-52. 14. Van Wessel D, Thompson R, Grammatikopoulos T, Kadaristiana A, Jankowska I, Lipinski P, et al. Factors associated with the natural course of disease in patients with FIC1-deficiency: The NAPPED-consortium. Journal of Pediatric Gastroenterology and Nutrition. 2019;68(Supplement 1):688-9.	

Section	Consultee/ Commentator	Comments [sic]	Action
		15. Karpen SJ, Kelly D, Mack C, Stein P. Ileal bile acid transporter inhibition as an anticholestatic therapeutic target in biliary atresia and other cholestatic disorders. Hepatology International. 2020:1-13. 16. Davit-Spraul A, Gonzales E, Baussan C, Jacquemin E. Progressive familial intrahepatic cholestasis. Orphanet journal of rare diseases. 2009;4(1):1. 17. Jacquemin E. Progressive familial intrahepatic cholestasis: genetic basis and treatment. Clinics in Liver Disease. 2000;4(4):753-63. 18. NHS England. Highly Specialised Services 2018 [Available from: https://www.england.nhs.uk/commissioning/wp-content/uploads/sites/12/2018/12/Highly-Specialised-Services-2018-v2.pdf. 19. NHS England. 2013/2014 NHS Standard Contract Specialist Liver Disease Service (Children) 2013 [Available from: https://www.england.nhs.uk/wp-content/uploads/2013/06/e03-speci-paedi-liver.pdf. 20. NHS England. 2013/14 NHS Standard Contract Paediatric Medicine: Gastroenterology, Hepatology and Nutrition 2013 [Available from: https://www.england.nhs.uk/wp-content/uploads/2013/06/e03-paedi-med-gastro-hepa-nut.pdf. . 21. Goldberg A, Mack CL. inherited Cholestatic Diseases in the era of Personalized Medicine. Clinical Liver Disease. 2020;15(3):105.	

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

None