NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

HIGHLY SPECIALISED TECHNOLOGY

Odevixibat for treating progressive familial intrahepatic cholestasis [ID1570]

The following documents are made available to the consultees and commentators:

1. **Response to consultee, commentator and public comments on the Evaluation Consultation Document (ECD)**

2. **Comments on the Evaluation Consultation Document from Albireo AB**
   - Company response
   - Company response appendix

3. **Consultee and commentator comments on the Evaluation Consultation Document** from:
   - Children's Liver Disease Foundation

4. **Comments on the Evaluation Consultation Document from experts:**
   - Prof Deirdre Kelly– clinical expert, nominated by Albireo AB
   - Dr Richard Thompson– clinical expert, nominated by Albireo AB
   - Claire Brinkley – patient expert, nominated by Children's Liver Disease Foundation

5. **Comments on the Evaluation Consultation Document received through the NICE website**
   - Comments received through the website
   - Comments received from PFIC network

6. **Evidence Review Group critique of company comments on the ECD**

Any information supplied to NICE which has been marked as confidential, has been redacted. All personal information has also been redacted.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Highly Specialised Technology Evaluation

Odevixibat for progressive familial intrahepatic cholestasis [ID1570]

Response to consultee, commentator and public comments on the Evaluation Consultation Document (ECD)

Definitions:

Consultees – Organisations that accept an invitation to participate in the appraisal including the manufacturer or sponsor of the technology, national professional organisations, national patient organisations, the Department of Health and relevant NHS organisations in England. Consultee organisations are invited to submit evidence and/or statements and respond to consultations. They are also have right to appeal against the Final Evaluation Determination (FED). Consultee organisations representing patients/carers and professionals can nominate clinical specialists and patient experts to present their personal views to the Evaluation Committee.

Clinical specialists and patient experts – Nominated specialists/experts have the opportunity to make comments on the ECD separately from the organisations that nominated them. They do not have the right of appeal against the FED other than through the nominating organisation.

Commentators – Organisations that engage in the evaluation process but that are not asked to prepare an evidence submission or statement. They are invited to respond to consultations but, unlike consultees, they do not have the right of appeal against the FED. These organisations include manufacturers of comparator technologies, Welsh Government, Healthcare Improvement Scotland, the relevant National Collaborating Centre (a group commissioned by the Institute to develop clinical guidelines), other related research groups where appropriate (for example, the Medical Research Council); other groups (for example, the NHS Confederation, and the *British National Formulary*).

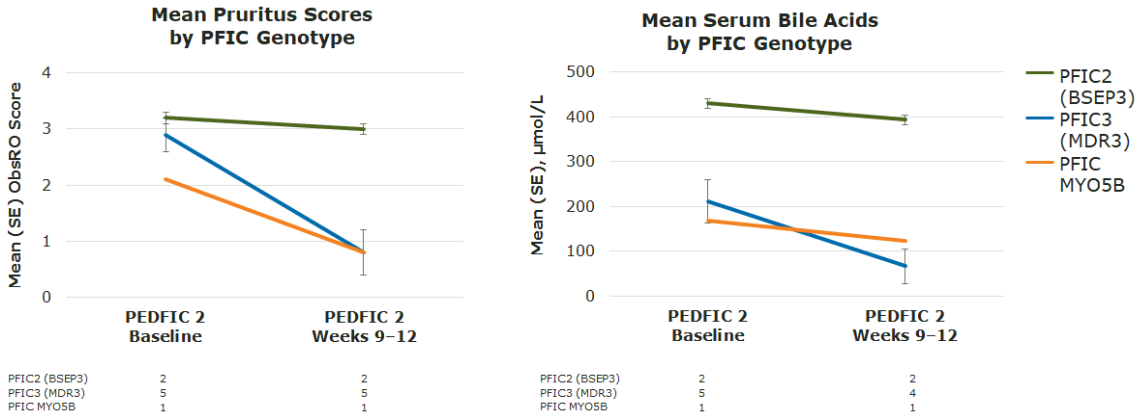
Public – Members of the public have the opportunity to comment on the ECD when it is posted on the Institute's web site 5 days after it is sent to consultees and commentators. These comments are usually presented to the evaluation committee in full, but may be summarised by the Institute secretariat – for example when many letters, emails and web site comments are received and recurring themes can be identified.

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.

Comments received from consultees

Consultee	Comment	Response
Albireo AB (company)	**1. Executive summary** Albireo appreciates the opportunity to provide additional evidence to address the uncertainties noted by the committee in the ECD. Overall, we felt that the ECD reflected the high unmet need in PFIC and the substantial impact of this progressive and debilitating condition on patients and their families, and provided a fair and balanced overview of the evidence. However, there remain uncertainties in the clinical and economic evidence base. Albireo has engaged with three clinical experts to discuss the key uncertainties raised in the ECD. The clinical experts were [redacted] as well as an additional clinical expert who is [redacted]. In this response, we provide further information to support the following two key points that are aligned with clinical expert opinion: • In line with the licensed indication, odevixibat should be made available for the treatment of all PFIC subtypes • The disutility of a stoma bag in children with PFIC is underestimated by the ERG's value: while still likely to underestimate the impact of a biliary stoma, the utility value from ulcerative colitis is more appropriate In addition to this, the criteria used to define an adequate clinical response and the need for dose escalation in clinical practice were confimed by the clinical experts. On the criteria used to define an adequate clinical response, the clinical experts all agreed with the description in the ECD, i.e., improvements in at least 2 of the 3 main PFIC outcomes: serum bile acid levels, pruritus and liver function tests. Regarding the need for dose escalation, the three clinical experts agreed that, based on the data available, it is reasonable to assume that [redacted] of patients would ultimately be treated at the higher	Thank you for your comment. Please see responses to individual comments below.

Consultee	Comment	Response
	dose. Albireo is currently in discussions with NICE PASLU and NHS England to explore commercial options that may address and alleviate the above uncertainities. Cost-effectiveness scenario analyses are presented to further explore the impact of stoma disutilites; rate of PEBD in the SoC arm and following odevixibat; rate of mortality after a second liver transplant; and productivity costs. These are provided in Appendix A.	
Albireo AB (company)	**2. Odevixibat should be made available for the treatment of all PFIC subtypes** In section 4.1 the ECD states that the committee "*concluded that the clinical effectiveness of odevixibat by PFIC type was uncertain*." Whilst this is true, we believe that odevixibat should be made available for the treatment of all PFIC subtypes in line with the licensed indication. According to the three clinical experts contacted, cases of PFIC 4, 5 and 6 are extremely rare in UK clinical practice; however they would like the ability to prescribe the best treatment for these patients if or when they present. The very low numbers of patients with these subtypes **worldwide** are reflected in the published literature. We identified all original papers and summarised the number of cases described worldwide for the period of 2013-2021: • 28 individuals with PFIC4 (TJP2-associated PFIC) have been described[1-5] • 9 cases of PFIC5 (NR1H4/FXR-associated PFIC) have been described[6-8] • 36 individuals with PFIC6 (MYO5B-associated PFIC) have been described[9-11] Odevixibat was granted marketing authorisation by the European Commission on July 16th 2021 with the indication for the treatment of progressive familial intrahepatic cholestasis (PFIC) in patients aged 6 months or older. All PFIC subtypes, regardless of the underlying genetic mutation, result in cholestasis characterised by elevated bile acid concentrations and intense pruritus. Odevixibat directly addresses the elevated serum bile acids and pruritus by inhibiting ileal bile acid transporters (IBAT) in the terminal ileum, transporters common to patients with all PFIC subtypes. The site of action of odevixibat is distal to the underlying biochemical abnormalities and is independent of the genetic abnormalities responsible for the different PFIC subtypes. Although limited, accumulating data provide a strong initial signal for efficacy in five patients with PFIC3 and demonstrate success in the patient with PFIC6 (Figure 1). Similarly, reductions in	Thank you for your comment. At the second meeting, the committee heard that odevixibat is expected to work in all PFIC types except PFIC5. Odevixibat is therefore recommended in all PFIC types except PFIC5. See FED section 4.18.

Consultee	Comment	Response
	serum bile acid levels were also observed in PFIC patients in the phase 2 study which included patients with PFIC1, PFIC2 and PFIC3 ( ). Reductions were seen in all patients except the PFIC2 patients with complete absence of BSEP which are excluded from our label and model. Considering the rarity of these subtypes, conducting a randomised, controlled clinical trial in these patients is extremely challenging and further collection of clinical data for these patients is only possible in long-term studies such as PEDFIC2 (ongoing) and the PFIC registry, which Albireo is committed to conduct. However, as with PFIC1 and PFIC2, there is a critical unmet medical need in all these populations. Based on the extremely low numbers of PFIC 4, 5 and 6 patients worldwide, this represents a minimal risk to the NHS and clinicians should have the option of treating all eligible PFIC patients. **Figure 1. Changes in pruritus and sBA observed in subtypes of patients in PEDFIC2**  	
Albireo AB (company)	**3. Disutility of a stoma bag in children with PFIC** In section 4.28 the ECD states that "*The committee agreed that the disutility of living with a stoma bag was likely to be lower than both the company and ERG's preferred values, but higher than the utility derived by the company's elicitation study. It would have preferred to see analyses*	Thank you for your comment. Based on clinical expert opinion at the second committee meeting, the committee updated its preferred assumptions to include the stoma bag

Consultee	Comment	Response
	using alternative stoma bag disutilities. However, it concluded that, in the absence of alternative sources, the ERG's utility value should be used for decision making." As part of the vignette study the clinical expert explained and described problems that children may experience with a biliary stoma (Company response to clarification - Addendum C). This included problems with the area around the stoma becoming sore or infected. The bags were unpleasant and could leak, especially at night. The clinical expert noted that PEBD can have a significant impact on the quality of life for adolescents as they become more conscious of their bodies and start having relationships. The company identified two sources for the disutility associated with PEBD. The first was in patients with ulcerative colitis (UC) which gave a multiplier of 0.72 and the second in patients with colorectal cancer (CC), which gave a multiplier of 0.945. The UC study was selected as it was felt to be more analogous and relevant to PFIC than the CC study. Patients in the CC study were predominantly over 70 and the comparison made was patients with a stoma versus those with a major bowel resection, which is also expected to have a serious impact on quality of life. Other confounding factors were identified that may impact the multiplier, such as ongoing post-surgical complications and high rates of bowel dysfunction in the comparator group. On the other hand, patients in the UC study were younger and the comparison used to calculate the multiplier was ileostomy versus remission, which was judged to be more relevant to the application in the economic model. As described in the ECD, "*the clinical experts explained that the stoma-related effect on quality of life is significant, especially in older children. This is because the disutility may be larger in them and they often refuse an external biliary diversion. The clinical expert also highlighted that stoma-related quality of life was likely to be better for someone with colorectal cancer or ulcerative colitis than for someone with a stoma bag collecting bile. This is because of problems arising from the irritant nature of bile. The patient experts highlighted that people with PFIC and carers have a very negative attitude to having a stoma bag."* Albireo has further consulted with three clinical experts (see point 1) who confirmed that the disutility value derived from ulcerative colitis is appropriate but is still likely to underestimate the impact of a biliary stoma. Based on this feedback we believe that the committee's preferred disutility value based on the average of the colorectal cancer and ulcerative colitis studies (0.833) understates the impact of PEBD and that the true value would be closer to or worse than that for ulcerative colitis (0.722). As such, the company's base-case analyses assume a value of 0.722 for the utility multiplier associated with PEBD.	utility multiplier from the ulcerative colitis study. See FED section 4.29.

Consultee	Comment	Response
	Further scenario analysis has been presented using the committee's preferred value (0.833) and the utility multiplier derived from the vignette study ([redacted]). See Appendix A.	
Albireo AB (company)	**4. Response criteria and dose escalation** ***Criteria for dose escalation/definition of response*** In section 4.17 the ECD states that "*it had not been possible to determine a real-life definition of an adequate clinical response or specific criteria for dose escalation. The clinical experts classed an adequate response to odevixibat as improvements in at least 2 of the 3 main PFIC outcomes: serum bile acid levels, pruritus and liver function tests. They acknowledged that a definition of response might vary among clinicians. However, they explained that the dose of odevixibat would likely be increased if little or no improvement in these outcomes was seen*." Following the committee meeting Albireo has engaged with three clinical experts (see point 1) who have confirmed that the definition of an adequate clinical response stated in the ECD would be used in practice to determine the response and the need for dose escalation. ***Estimation of proportion of patients requiring dose escalation*** In section 4.20 the ECD states that *"The committee concluded that there was significant uncertainty* *surrounding the proportion of people having high-dose odevixibat and the serum bile acid response in these people."* It is difficult to predict with certainty the proportion of patients who will receive the higher dose of odevixibat. The definition of an adequate clinical response to be used in practice, as described above, is less stringent than that used in the clinical trials and economic model, where an sBA response was defined as a change from baseline to ≤70 µmol/L or a reduction of 70% after 72 weeks of treatment. Therefore, fewer patients are expected to require dose escalation than is currently estimated in the economic model based on sBA data from PEDFIC1, where 56.5% of patients did not achieve an sBA response to the lower dose (primary endpoint analysis).[12] In addition to the evidence already included in the company submission and provided during clarification, Albireo has discussed the topic of the proportion of patients that would be treated and remain on treatment on the 120mcg/kg/dose with the three clinical experts. Although there remains uncertainty on the proportion of patients who would be treated on the higher dose in clinical practice, the three clinical experts agreed that, based on the data available, it is	Thank you for your comments. The FED has been updated to describe the company's preference for the response criteria in the ECD. See FED section 4.17. At the second committee meeting the committee agreed that the company's assumptions about high-dose odevixibat in the model were uncertain but acceptable for decision making. See FED section 4.20.

Consultee	Comment	Response
	reasonable to assume that [redacted]% of patients would ultimately be treated at the higher dose. Albireo is also in discussions with NICE PASLU and NHS England to explore commercial options that may address and alleviate this issue. Please see point 7.	
Albireo AB (company)	**5. PEBD as an option in the odevixibat arm** In section 4.22 the ECD states that "*It concluded that PEBD should have been included in both arms. It also concluded that the rates should be considered in exploratory analyses, if possible, informed by a data source that was clinically relevant to the NHS".* The NAPPED database in considered the most clinically relevant international data source for informing the rates of PEBD. It includes data from three specialist centres in England; however, no data documenting the rate of biliary diversion surgery in the UK were identified. In the SoC arm of the model when NAPPED data is used to inform the rate of PEBD surgery, 32% of patients undergo a PEBD and the company acknowledges that this figure may be too high. The rates of PEBD surgery in patients who have previously been treated with odevixibat are unknown; however, based on clinical input this rate is expected to be much lower than in the SoC arm. During the committee meeting, one of the clinical experts stated that rates of PEBD in England are low and would be even lower after odevixibat. In an advisory board attended by nine UK clinical experts, all experts agreed that the treatment pathway models for PFIC1 and PFIC2 proposed by Albireo for the company submission were representative of their practices.[13] The clinical experts concurred with the positioning of odevixibat in the treatment pathway and stated that they would not usually expect to use PEBD following odevixibat treatment. However, NICE and the ERG received expert clinical advice that suggested that PEBD surgery could be offered to those who did not respond on odevixibat. We agree that in principle there is the potential for PEBD to be used after odevixibat; however, even if this were to happen it is expected to be at a much lower rate than in current clinical practice in the absence of odevixibat. The company's updated base-case analysis follows the committee's preferences for modelling PEBD surgery. The rates from NAPPED are used in the base-case and PEBD is assumed to occur at the same rate in the non-responders to odevixibat as in the SoC arm. However, based on clinician advice that these rates may be higher than are seen in clinical practice, and that the rate among patients who have previously received odevixibat may be lower, the scenarios shown in the table below are also included. Crosses indicate a modelled scenario.	Thank you for your comment. The committee considered scenarios varying the rate of PEBD. However, at the second meeting, following additional clinical expert opinion, it agreed that PEBD was unlikely to be offered after odevixibat so should not be included in the intervention arm. In the absence of further data sources for the standard care arm, it agreed that rates from NAPPED study should be used in the model. See FED section 4.6 and 4.22.

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<tr><th>Consultee</th><th>Comment</th><th>Response</th></tr>
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<table>
<tr><td colspan="2"></td><td colspan="4">Rate of PEBD in the SoC arm</td></tr>
<tr><td colspan="2"></td><td>Base-case</td><td>50% reduction</td><td>75% reduction</td><td>90% reduction</td></tr>
<tr><td rowspan="5">Rate of PEBD in the odevixibat arm</td><td>Base-case</td><td>X</td><td></td><td></td><td></td></tr>
<tr><td>50% reduction</td><td>X</td><td>X</td><td></td><td></td></tr>
<tr><td>75% reduction</td><td>X</td><td>X</td><td>X</td><td></td></tr>
<tr><td>90% reduction</td><td>X</td><td>X</td><td>X</td><td>X</td></tr>
<tr><td>No PEBD</td><td>X</td><td>X</td><td>X</td><td>X</td></tr>
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<tr><td>Albireo AB (company)</td><td>6. Rate of mortality after second transplant

During the committee meeting, it was raised that the mortality risk following a second transplant was higher than following a first. Watt et al 2010[14] explored risk factors for mortality post liver transplant and found retransplant to be associated with a higher risk of death beyond 1 year post-transplant. Patients that were retransplanted within 1 year had a mortality hazard ratio of 1.52 and patients retransplanted beyond 1 year had a hazard ratio of 4.79.

Scenarios have been included to explore higher rates of post-transplant mortality for patients that have been retransplated. In these scenarios, the probability of death beyond 1 post-transplant is weighted by proportion of patients that have undergone more than 1 transplant. The first scenario assumes all retransplants occur within 1 year and applies a hazard ratio of 1.52. The second assumes they all happen beyond year 1 and applies a hazard ratio of 4.79.</td><td>Thank you for your comment. The committee considered the company's scenarios using a higher risk of death for the second transplant compared with the first. It agreed that neither of the scenarios captured both the increased risk of death from a later retransplant and the increased chance of retransplant within the first year after initial surgery simultaneously. The committee preferred to apply a hazard ratio of 4.79 to the proportion of people having more than one transplant, but only in the first year in the model. See FED section 4.25.</td></tr>
<tr><td>Albireo AB (company)</td><td>7. Options to address and alleviate the cost-effectiveness uncertainties

Albireo are in discussions with NICE PASLU and NHS England around commercial options that may further address the cost-effectiveness uncertainties. Albireo [redacted]</td><td>Thank you for your comment. The committee took the patient access scheme (PAS) into account when it considered the cost-effectiveness results.</td></tr>
<tr><td>Albireo AB</td><td>8. Odevixibat is expected to have further impact outside of the NICE reference case</td><td>Thank you for your comment. The committee agreed that PFIC affects</td></tr>
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Consultee	Comment	Response
(company)	The company accepts that carer productivity costs are outside of the NICE reference case, however we maintain that these results reflect the important impact that odevixibat may have beyond the direct health benefits for patients and should be taken into account when appraising the cost-effectiveness of odevixibat. As evidenced by the results of the PICTURE study, [redacted]. In the ECD carers explained that "*they needed to provide constant care to children with PFIC. Commonly, the demands are such that carers cannot work full time, resulting in loss of earnings and implications for career development. One carer explained that she could no longer carry on with her job as her daughter deteriorated because of the demands of juggling hospital visits and sleepless nights.*" A scenario analysis including these costs has been included.	patients beyond the direct health benefits. It concluded that the full disadvantages of the comparator treatments and mental and physical impact on carers of people with PFIC may not be fully captured in the company's modelling. It considered these uncaptured benefits in its decision making. See FED sections 4.37, 4.44 and 4.45
Children's Liver Disease Foundation	**1. Unmet need and no other treatment options available:** This is an unmet need with no alternative, comparative, non-surgical treatment available specifically for PFIC. Off label treatments may support with aspects such as pruritus and vitamins and dietetic services can support with nutrition but with varying degrees of success. Many rely on practical solutions unless/until it reaches the point of liver transplantation which carries a high level of risk. While there are other treatments being trialled in this cohort of patients this is the only drug in the pipeline for PFIC patients in the near future.	Thank you for your comment. The committee recognised that treatment options for PFIC are currently limited. It concluded that there was an unmet need for a new treatment for this condition. See FED section 4.4.
Children's Liver Disease Foundation	**2. There was agreement that it has an impact beyond direct health benefits. However, we have provided some comments below regarding the committee responses to this area:** Surgeries (transplant and biliary diversion) have greater impact on the whole family in a variety of ways. There are not only financial implications but mental health and psychological impact on the child as well as the parents and siblings also need to be considered. Furthermore, there will be greater time spent away from other children/siblings/partners in these circumstances which increases anxieties and effects relationships. This drug may reduce the number of visits necessary because of a potential reduction in pruritus, its effects, and the need to manage these. Of course, they will still need to attend appointments to monitor the condition but the number of visits outside of follow up and general management appointments could potentially be reduced. Delay the time to transplant – liver transplant may be needed at some stage but there are	Thank you for your comment. The committee agreed that PFIC affects patients beyond the direct health benefits. It concluded that the full disadvantages of the comparator treatments and mental and physical impact on carers of people with PFIC may not be fully captured in the company's modelling. It considered these uncaptured benefits in its decision making. See FED sections 4.37, 4.44 and 4,45

Consultee	Comment	Response
	benefits to attempting to delay this and keep the child's native liver as long as possible. It may reduce the need to be on immunosuppressants until as late as possible and the associated effects. The risks of surgery are great as well as the increased risk of infections and viruses due to immunosuppressants and risk of cancer (PTLD). Transplantation also reduces the sports and social activities they can get involved in (e.g. contact sports) and careers they can undertake (roles that involve increased exposure to infections and/or heavy lifting/contact). Transplant although lifesaving is not a cure, those patients need a lifetime of care. The ongoing immunosuppression not only has its own risks in the longer term, the child and family live with the ongoing concern that the new liver may fail at some stage leading to the need for further lifesaving transplants. The goal for most families and professionals is for a child to live with their native liver for as long as possible.	
Children's Liver Disease Foundation	**3. Uncertainties:** Uncertainty is a characteristic of rare diseases, in particular a complex organ such as liver, but even more complex in children compared to adults. How each patient is impacted and to what extent varies considerably. Regarding some of the uncertainties raised in the ECD, it would require paediatric hepatology services restructure in terms of databases, policy and processes and much increased levels of research to overcome some of these which will take many years due to the little resource this field has in terms of specialists, researchers and patient numbers. In relation to other subgroups, PFIC 1 and 2 are the most common in children and form the majority of PFIC diagnoses. Therefore, according to the committee recommendations, the majority will lose out because of insufficient evidence for much rarer sub-groups where recruiting patients will be considerably more difficult.	Thank you for your comment. The committee acknowledged the challenges of further data collection in PFIC made data collection outside of the existing studies implausible. However, it noted that existing studies were still ongoing. At the second meeting, the committee heard that odevixibat is expected to work in all PFIC types except PFIC5. Odevixibat is therefore recommended in all PFIC types except PFIC5. See FED section 4.18 and 6.
Children's Liver Disease Foundation	**4. Final overview:** This is an unmet need with no alternative comparative non-surgical treatment available specifically for PFIC. Uncertainties are common in research and trials with rare disease patients particularly children with small cohorts of patient groups in a variety of subgroups. The overall assessment of NICE in terms of clinical effectiveness was that, in the time of trial, it had positive outcomes for a number of patients in that it was effective in reducing both serum bile acids and pruritus in both PFIC 1 and 2. This seems to indicate it is clinically effective. By not approving this technology the benefits patients could gain in the short term are being obstructed due to lack of long-term data which will take many years. There is an urgency for treatment now with no other drugs in the pipeline for this condition.	Thank you for your comment. No further action required.

Consultee	Comment	Response
	There is currently no other treatment available for these patients so any benefit they could gain (short/long term) from being prescribed this medication as a step before transplant to be able to manage symptoms and side effects would be advantageous to not only the child but their whole family. Quality of life would be considerably improved with the potential to reduce serum bile acid levels and pruritus. Below comment from PFIC family: "I looked after my grandson on a few occasions in the early days after his diagnosis with this disease. It was heart breaking to watch him always crying and covered in blood from scratching his skin off. He could not participate in any normal childhood activities and was either crying or sleeping. The medication trial was then offered to him and within months the improvement in his health and quality of life was incredible he became a different child and to any who did not know his story he was a normal healthy child."	

Comments received from clinical specialists and patient experts

Nominating organisation	Comment	Response
Birmingham Women' & Children's Hospital	1. Page 3. There are few data on treatment with or without Odevixabat in other types of PFIC because it is a rare disease and Types 1 & 2 are the most common. It would be impossible to carry out clinical trials and add to the data on other types of PFIC	Thank you for your comment. The committee agreed that the practical challenges of recruiting people with the rarer types of PFIC to clinical trials made data collection outside of the existing studies implausible. However, it noted that existing studies were still ongoing. See FED section 4.18 and 6.
Birmingham Women' & Children's Hospital	2. Page 7 Agree the effect of Odevixabat on QoI in affected patients and families is significant & there is unmet need	Thank you for your comment. The committee agreed that PFIC has a significant effect on the quality of life of people with the condition, family members and carers. It acknowledged there was an unmet need for a new treatment for this condition. See FED section 4.2 and 4.4.
Birmingham Women' & Children's Hospital	3. Page 9 - 4.5. Agree pathway of care is determined by type of PFIC, but Odevixabat may improve QoL, pruritus and liver function in any of the types evaluated	Thank you for your comment. At the second meeting, the committee heard that odevixibat is expected to work in all PFIC types except PFIC5. Odevixibat is therefore recommended in all PFIC types except PFIC5. See FED section 4.18

Nominating organisation	Comment	Response
Birmingham Women' & Children's Hospital	4. Page 9 – 4.6 SBD is not standard of care in UK and is only an alternative to PFIC 1 because the disease is not curable with Tx and S/E post-transplant (diarrhoea etc) are debilitating. If no response to Odevixabat, then SBD is unlikely to work. Off label medications are current standard of care	Thank you for your comment. At the second meeting, following additional clinical expert opinion, the committee agreed that PEBD was unlikely to be offered after odevixibat so should not be included in the intervention arm. See FED section 4.6 and 4.22.
Birmingham Women' & Children's Hospital	5. Page 14 – 4.12 There are few data on treatment with or without Odevixabat in other types of PFIC because it is a rare disease and Types 1 & 2 are the most common. It would be impossible to carry out clinical trials and add to the data on other types of PFIC	Thank you for your comment. The committee agreed that the practical challenges of recruiting people with the rarer types of PFIC to clinical trials made data collection outside of the existing studies implausible. However, it noted that existing studies were still ongoing See FED section 4.16 and 6
Birmingham Women' & Children's Hospital	6. Page 17 -4.17. It is difficult to make a recommendation on dose escalation in view of the design of the studies. In practice, patients would start on the lower dose and the dose would only be escalated if there was an insufficient response using the parameters agreed in 3 months. It is likely that only 30% patients of need the highest dose.	Thank you for your comment. At the second committee meeting the committee agreed that the company's assumptions about high-dose odevixibat in the model were uncertain but acceptable for decision making. See FED section 4.20.
Birmingham Women' & Children's Hospital	7. Page 19 – 4.19. I do not agree that SBD should be included as an option in the treatment arm as If no response to Odevixabat, then SBD is unlikely to work	Thank you for your comment. At the second meeting, following additional clinical expert opinion, the committee agreed that PEBD was unlikely to be offered after odevixibat so should not be included in the intervention arm. See FED section 4.6 and 4.22.
Birmingham Women' & Children's Hospital	8. Page 25 – 4.31. Difficult to apply standard QALYs developed in adults to infants with a rare disease	Thank you for your comment. A QALY weighting of between 1 and 3 can be applied to ICERs above a most plausible incremental cost-effectiveness ratio (ICER) of £100,000 per QALY gained for technologies with compelling evidence of significant health benefits. This process is unique to Highly Specialised Technologies for rare conditions, many of which occur in children. See NICE's interim process and methods of the highly specialised technologies programme (2017) for further information.

Nominating organisation	Comment	Response
Richard John Thompson	1. I believe that the similarity of the mechanism of action of odevixibat and SBD have been underestimated. I believe that has had effects on the modelling. Both forms of treatment seek to interrupt the enterohepatic circulation of bile acids, after export from the liver. The purpose of this measure if to reduce the bile salt pool size, and critically to reduce the requirement for the liver to transport bile acids. If this requirement is reduced to a level below the capacity of the liver to transport bile acids then the primary problem has been overcome. This concept applies to all forms of PFIC identified so far, except MDR3 and FXR deficiencies. The latter is not expected to respond, however the former is biologically an excellent candidate, although there is no intrinsic problem with bile salt transport. Instead the problem is of damage to the liver by effectively transported bile acids. Reduction in bile salt flux through the liver, in MDR3 deficiency, will reduce the concentrations of bile salts in bile, and therefore reduce the damage. MDR3 is quite different in this respect from the other forms of PFIC in this respect.	Thank you for your comment. At the second meeting, the committee heard that odevixibat is expected to work in all PFIC types except PFIC5. Odevixibat is therefore recommended in all PFIC types except PFIC5. See FED section 4.18.
Richard John Thompson	2. Because the mechanism of action of odevixibat is so close to the intention of SBD I believe the modelling does need some further thought. Both forms of treatment have the potential to radically transform the natural history of PFIC and completely remove the need for transplantation, in those patients where the treatment is successful. Following on from the above, the intended reduction in the requirement for bile acid transport, will prevent the accumulation of bile acids in the liver, prevent progressive liver damage, significantly reduce the pruritus and as a secondary consequence reduce serum bile acid levels in peripheral blood. Please note that it is bile acid levels in the liver that are damaging, and almost certainly lead to pruritus. Peripheral blood levels are an indirect, although clinically available, measure.	Thank you for your comment. At the second meeting, following additional clinical expert opinion, the committee agreed that PEBD was unlikely to be offered after odevixibat so should not be included in the intervention arm. See FED section 4.6 and 4.22.
Richard John Thompson	3. The NAPPED studies, of which the committee are very aware, are critical in showing that reduction in serum bile acids (although an indirect marker), after interruption of the enterohepatic circulation of bile acids, are predictive of transplant avoidance in both FIC1 and BSEP deficiencies. As the committee noted, SBD is not an ideal treatment for many reasons. Not only is it disfiguring and psychologically problematic, it also predisposes to electrolyte disturbance and cholangitis. The proportion of bile acids diverted is always very unclear.	Thank you for your comment. The committee agreed that PEBD is associated with a decrease in serum bile acid levels and increased native liver survival. It also acknowledged the risks of complications and significant effect on quality of life from a stoma bag. See FED section 4.3 and 4.29.

Nominating organisation	Comment	Response
Richard John Thompson	4. I believe that SBD should be used as a comparator in the modelling.	Thank you for your comment. The committee agreed that SBD, including PEBD, was a relevant comparator. See FED section 4.6.
Richard John Thompson	5. I believe that the NAPPED data indicate that effective depletion of bile acids dramatically changes the natural history of these diseases.	Thank you for your comment. The committee acknowledged that lower serum bile acid levels are generally associated with improved pruritus and native liver survival. See FED section 4.10.
Richard John Thompson	6. I have looked after a lot of patients with PFIC. It is a devastating disease. The pruritus destroys patient's and families' lives. Liver transplant is a very good treatment for BSEP deficiency. But has considerable short and long term risk, as noted by the committee. It is not a good treatment for FIC1 deficiency, as it frequently makes the gastrointestinal symptoms worse. However the fact that families are very prepared to put their children's lives at considerable risk (by subjecting them to transplantation) in order to overcome the pruritus, tells you everything you need to know about the awfulness of this symptom, in this disease.	Thank you for your comment. The committee recognised that PFIC is a highly debilitating disease and that treatment options for PFIC are currently limited. It concluded that there was an unmet need for a new treatment for this condition. See FED section 4.2 and 4.4.
Richard John Thompson	7. I think that I understand the constraints of the NICE modelling, though it is far from my area of expertise. Somehow the process seems to have underestimated the life changing effect that this treatment has had on both children with PFIC and their families.	Thank you for your comment. The committee agreed that PFIC affects patients beyond the direct health benefits. It concluded that the full disadvantages of the comparator treatments and mental and physical impact on carers of people with PFIC may not be fully captured in the company's modelling. It considered these uncaptured benefits in its decision making. See FED sections 4.37, 4.44 and 4.45.
Claire Brinkley	1. As a parent of a PFIC child, I cannot express strongly enough how much of a difference this drug would make. Transplant is not an acceptable treatment for children. It is unbelievably traumatic and not a cure. The impact of the itch on the child's quality of life is huge. It feels akin to physical abuse to allow a child to suffer in this way, scream through the night and rip their skin until it bleeds, then unable to learn in school as a result, when there is a medication that could prevent all of this.	Thank you for your comment. The committee recognised that PFIC is a highly debilitating disease with substantial effects on both physical and psychological aspects of quality of life. See FED section 4.2.

Comments received from commentators

Commentator	Comment	Response
	None received	

Summary of comments received from members of the public

Theme	Response
Do not agree with the ECD decision to not recommend odevixibat	Thank you for your comments. At the second committee meeting, the committee discussed responses to the ECD and the company's revised base case. It recommended odevixibat for use in people with all PFIC subtypes in the marketing authorisation except PFIC5. See FED section 1.1.
Nature of the disease	
Highly debilitating disease, with severe impact on patients' quality of life	Thank you for your comments. The committee recognised that PFIC is a highly debilitating disease with substantial effects on both physical and psychological aspects of quality of life. See FED section 4.2.
Pruritus traumatic for patients: relentless with no relief	Thank you for your comments. The committee recognised the debilitating impact of pruritus and its substantial effect on both physical and psychological aspects of quality of life for people with PFIC and their carers. See FED section 4.2.
Impact on education: missed school, decreased social interaction with associated mental health implications	Thank you for your comments. The committee recognised that PFIC has a substantial effect on quality of life which can impact a child's regular attendance at school, leading to reduced educational attainment and social development. See FED section 4.2.
Impact for carers and families	
Impact on employment for carers as forced to quit work to provide care. Financial and career progression implications.	Thank you for your comments. The committee was aware of the considerable quality of life impact on carers of people with PFIC. It acknowledged that the that mental and physical impact on carers of people with PFIC may not be fully captured in the company's modelling and considered this in its decision making. See FED section 4.2
Impact on mental health for carers: depression, stress and anxiety about disease progression or finances	Thank you for your comments. The committee recognised that PFIC is a highly debilitating disease with substantial effects on psychological aspects of quality of life. It acknowledged that the that mental impact on carers of people with PFIC may not be fully captured in the company's modelling and considered this in its decision making. See FED section 4.2, 4.37 and 4.45.

Theme	Response
Constant disruption to lives of whole family, including siblings: exhaustion due to broken sleep, constant fear of deterioration, frequent hospital visits	Thank you for your comments. The committee understood that children with PFIC need significant carer support, which can have a considerable effect on the quality of life of families. It acknowledged that the that mental and physical impact on carers of people with PFIC may not be fully captured in the company's modelling and considered this in its decision making. The FED has been amended to detail that exhaustion affecting the whole family is common in PFIC. See FED section 4.37.
Treatment pathway	
High unmet need for new PFIC treatments	Thank you for your comments. The committee recognised that treatment options for PFIC are currently limited. It concluded that there was an unmet need for a new treatment for this condition. See FED section 4.4.
Existing treatments extremely limited and invasive: not reflected fully in utilities	Thank you for your comments. The committee noted that there are no medicines licensed for PFIC in the UK. It considered the invasive nature of comparator treatments in its decision making. See FED section 4.3, 4.4 and 4.45.
Surgical biliary diversion does not always fully resolve itching	Thank you for your comments. The committee acknowledged that surgical biliary diversion does not always resolve pruritus. See FED section 4.29.
Stoma bag a great discomfort and shameful for patients and associated with risk of dehydration	Thank you for your comments. The committee was aware that the stoma-related effect on quality of life is significant, especially in older children. At the second meeting, the committee heard that a stoma bag can be distressing and can have a significant effect on quality of life as well as risk of complications such as leakage. The FED has been updated to further detail these complications. See FED section 4.3 and 4.29.
No long-term treatments for people with PFIC1, in whom transplant is less successful	Thank you for your comments. The committee was aware that the current pathway of care for people with PFIC varies depending on type and that liver transplant less likely to be offered to people with PFIC1. See FED section 4.5.
Transplant associated with short and long-term risks: immunosuppression, lost school days, limitations to daily activities (e.g. sports and social activities), increased risk of infections and cancer.	Thank you for your comments. At the second evaluation meeting the committee heard that transplant can negatively impact a child's social development because of lost school days for surgery and the inability to participate in activities or careers associated with high risks of infection. Section 4.4 and 4.37 of the FED have been updated in line with this comment.
Psychological impact of surgery (SBD and transplant) on patients and families not fully appreciated by committee.	Thank you for your comments. At the second evaluation meeting the committee acknowledged that surgeries such as transplant can have a psychological impact on the whole family. Section 4.4 of the FED has been updated in line with this comment.
Clinical effectiveness	
Evidence from trials that odevixibat reduces serum bile acids and improves pruritus in PFIC1 and 2	Thank you for your comments. The committee concluded that odevixibat was effective in reducing both serum bile acid level and pruritus in PFIC1 and PFIC2. See FED section 4.11.

Theme	Response
Recommendation should apply to all subtypes: implausible to collect further data in rarer subtypes	Thank you for your comments. The committee recognised the practical challenges of recruiting people with the rarer types of PFIC to clinical trials. At the second meeting, the committee heard that odevixibat is expected to work in all PFIC types except PFIC5. Odevixibat is therefore recommended in all PFIC types except PFIC5. See FED section 4.18.
Response (and need for dose escalation) determined by patient/carer reported improvements in itch: continue treatment whilst itch improving.	Thank you for your comments. The committee agreed that the dose of odevixibat would be increased if little or no improvement was seen in at least 2 of serum bile acid levels, pruritus and liver function tests. See FED section 4.17
Challenging to collect larger scale data in PFIC (any type), both in randomized controlled trials and clinical practice	Thank you for your comments. The committee was aware that PFIC is a rare disease and acknowledged the practical challenges of recruiting people to clinical trials made data collection outside of the existing studies implausible. See FED section 4.16.
Experience of using odevixibat	
Odevixibat can significantly improve patients' quality of life: reducing severity of pruritus, improving health and stabilising liver disease	Thank you for your comments. The committee considered that odevixibat was innovative and acknowledged that it is the first drug to both improve pruritus and limit progression of liver disease. See FED section 4.38.
Odevixibat can allow children to attend school regularly: improves education and social skills, improves career prospects	Thank you for your comments. At the second evaluation meeting, the committee noted that a reduction in pruritus would allow people with PFIC to attend school regularly, improving their education, career prospects and social skills. Section 4.36 of the FED has been updated in line with this comment.
Odevixibat can have a positive impact on mental health of patients, carers and families	Thank you for your comments. The committee was aware that odevixibat could lessen the psychological effect of the condition for people with PFIC, carers and siblings. See FED section 4.36.
Odevixibat can reduce the frequency of hospital visits: no additional safety monitoring required	Thank you for your comments. The committee was aware that odevixibat could lessen the number of hospital visits needed and that no additional safety monitoring is needed. See FED section 4.36 and 4.37.
Odevixibat is an oral drug: non-invasive and easy, could be administered locally under supervision	Thank you for your comments. The committee was aware that odevixibat is easy to administer in capsule form and can be sprinkled on to food for younger children. It acknowledged comments by the NHS England representative that odevixibat would be started at specialist centres, with the potential to consider monitoring by local healthcare providers if safe and useful. See FED section 4.37 and 4.38
NICE processes	

Theme	Response
Full savings from delays to, or reduced need for, transplant, along with cost of long-term immunosuppression and mental health support should be considered in model	Thank you for your comments. In accordance with the NICE guide to the interim process and methods of the Highly Specialised Technologies Programme (point 43) the committee considered whether a substantial proportion of the costs (savings) or benefits are incurred outside of the NHS and personal and social services. The committee agreed that PFIC affects patients beyond the direct health benefits. It concluded that the full disadvantages of the comparator treatments and mental and physical impact on carers of people with PFIC may not be fully captured in the company's modelling. It considered these uncaptured benefits in its recommendation. See FED sections 4.37, 4.44 and 4.45
Recommendation should be postponed until company's indirect treatment comparison available	Thank you for your comments. The committee was aware that the company's planned indirect comparison would provide data on the effectiveness of odevixibat compared with PEBD. It agreed results of the company's analysis would be useful to see at the time of the next guidance review. See FAD sections 4.36 and 6.1.
Uncertainties could be resolved by further data collection: rejection of managed access agreements should be reconsidered	Thank you for your comments. The committee agreed that some of the clinical uncertainties could be resolved with further data collection. It recalled that results from the company's extension study and indirect treatment comparison were expected in the near future and agreed this data would be useful at the time of the next guidance review. See FAD section 4.36 and 6.1.
Committee's focus should be on benefits not costs	Thank you for your comments. The committee discussed the need to balance the importance of improving the lives of people with PFIC and their families. It agreed that the company's model had not captured health-related benefits from delaying or stopping lifelong immunosuppression after transplant and impact on carers, the invasive nature of comparator treatments, the young age at which the condition develops, and the innovative nature of the treatment. After taking all of this into account, the committee recommended odevixibat for use in the NHS.

NICE National Institute for Health and Care Excellence

Odevixibat for treating progressive familial intrahepatic cholestasis [ID1570]

Consultation on the appraisal consultation document – deadline for comments 5pm on Thursday 07 October. Please submit via NICE Docs.

	Please read the checklist for submitting comments at the end of this form. We cannot accept forms that are not filled in correctly. The Appraisal Committee is interested in receiving comments on the following: • has all of the relevant evidence been taken into account? • are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence? • are the provisional recommendations sound and a suitable basis for guidance to the NHS? 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 preliminary recommendations may need changing in order to meet these aims. In particular, please tell us if the preliminary recommendations: • could have a different impact on people protected by the equality legislation than on the wider population, for example 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 provide any relevant information or data you have regarding such impacts and how they could be avoided or reduced**.**
Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	Albireo AB
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	Albireo has no direct or indirect links to, or funding from, the tobacco industry.
Name of commentator person completing form:	Maria Hall, Vice President, Global Market Access

NICE National Institute for Health and Care Excellence

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Comment number	Comments Insert each comment in a new row. Do not paste other tables into this table, because your comments could get lost – type directly into this table.
1	**Executive summary** Albireo appreciates the opportunity to provide additional evidence to address the uncertainties noted by the committee in the ECD. Overall, we felt that the ECD reflected the high unmet need in PFIC and the substantial impact of this progressive and debilitating condition on patients and their families, and provided a fair and balanced overview of the evidence. However, there remain uncertainties in the clinical and economic evidence base. Albireo has engaged with three clinical experts to discuss the key uncertainties raised in the ECD. The clinical experts were 'academic / commercial in confidence information removed' as well as an additional clinical expert who is 'academic / commercial in confidence information removed. In this response, we provide further information to support the following two key points that are aligned with clinical expert opinion: • In line with the licensed indication, odevixibat should be made available for the treatment of all PFIC subtypes • The disutility of a stoma bag in children with PFIC is underestimated by the ERG's value: while still likely to underestimate the impact of a biliary stoma, the utility value from ulcerative colitis is more appropriate In addition to this, the criteria used to define an adequate clinical response and the need for dose escalation in clinical practice were confimed by the clinical experts. On the criteria used to define an adequate clinical response, the clinical experts all agreed with the description in the ECD, i.e., improvements in at least 2 of the 3 main PFIC outcomes: serum bile acid levels, pruritus and liver function tests. Regarding the need for dose escalation, the three clinical experts agreed that, based on the data available, it is reasonable to assume that [redacted] of patients would ultimately be treated at the higher dose. Albireo is currently in discussions with NICE PASLU and NHS England to explore commercial options that may address and alleviate the above uncertainities. Cost-effectiveness scenario analyses are presented to further explore the impact of stoma disutilites; rate of PEBD in the SoC arm and following odevixibat; rate of mortality after a second liver transplant; and productivity costs. These are provided in Appendix A.
2	**Odevixibat should be made available for the treatment of all PFIC subtypes** In section 4.1 the ECD states that the committee "*concluded that the clinical effectiveness of odevixibat by PFIC type was uncertain*." Whilst this is true, we believe that odevixibat should be made available for the treatment of all PFIC subtypes in line with the licensed indication. According to the three clinical experts contacted, cases of PFIC 4, 5 and 6 are extremely rare in UK clinical practice; however they would like the ability to prescribe the best treatment for these patients if or when they present.

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The very low numbers of patients with these subtypes **worldwide** are reflected in the published literature. We identified all original papers and summarised the number of cases described worldwide for the period of 2013-2021:

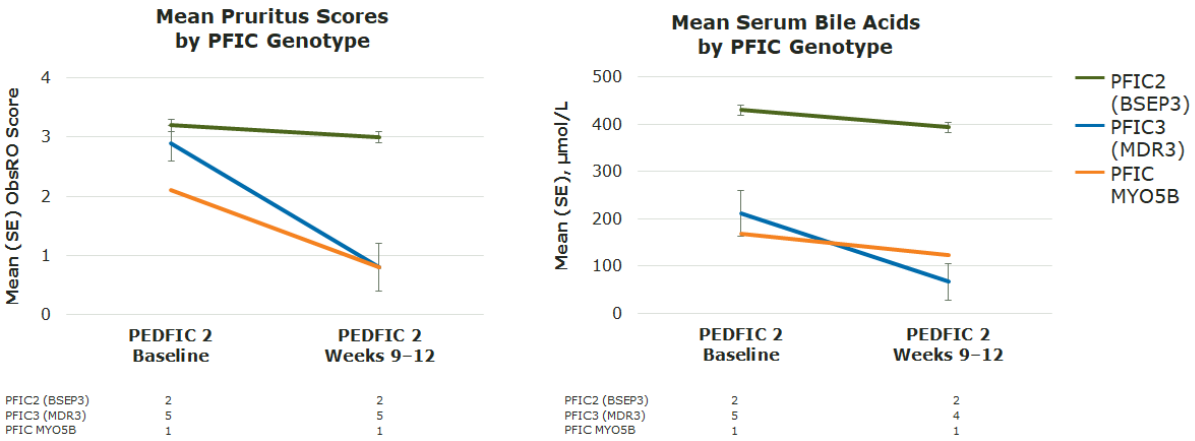
- 28 individuals with PFIC4 (TJP2-associated PFIC) have been described[1-5]
- 9 cases of PFIC5 (NR1H4/FXR-associated PFIC) have been described[6-8]
- 36 individuals with PFIC6 (MYO5B-associated PFIC) have been described[9-11]

Odevixibat was granted marketing authorisation by the European Commission on July 16th 2021 with the indication for the treatment of progressive familial intrahepatic cholestasis (PFIC) in patients aged 6 months or older. All PFIC subtypes, regardless of the underlying genetic mutation, result in cholestasis characterised by elevated bile acid concentrations and intense pruritus. Odevixibat directly addresses the elevated serum bile acids and pruritus by inhibiting ileal bile acid transporters (IBAT) in the terminal ileum, transporters common to patients with all PFIC subtypes. The site of action of odevixibat is distal to the underlying biochemical abnormalities and is independent of the genetic abnormalities responsible for the different PFIC subtypes.

Although limited, accumulating data provide a strong initial signal for efficacy in five patients with PFIC3 and demonstrate success in the patient with PFIC6 (Figure 1). Similarly, reductions in serum bile acid levels were also observed in PFIC patients in the phase 2 study which included patients with PFIC1, PFIC2 and PFIC3 (
). Reductions were seen in all patients except the PFIC2 patients with complete absence of BSEP which are excluded from our label and model.

Considering the rarity of these subtypes, conducting a randomised, controlled clinical trial in these patients is extremely challenging and further collection of clinical data for these patients is only possible in long-term studies such as PEDFIC2 (ongoing) and the PFIC registry, which Albireo is committed to conduct. However, as with PFIC1 and PFIC2, there is a critical unmet medical need in all these populations. Based on the extremely low numbers of PFIC 4, 5 and 6 patients worldwide, this represents a minimal risk to the NHS and clinicians should have the option of treating all eligible PFIC patients.

Figure 1. Changes in pruritus and sBA observed in subtypes of patients in PEDFIC2



Odevixibat for treating progressive familial intrahepatic cholestasis [ID1570]

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	Figure 2. Change from baseline in serum bile acids at the end of the 4-week treatment period (subgroup of patients with PFIC* in the phase 2 study) **'academic / commercial in confidence information removed'** *PFIC1 n=2; PFIC2 n=9; PFIC3 n=2
3	**Disutility of a stoma bag in children with PFIC** In section 4.28 the ECD states that "*The committee agreed that the disutility of living with a stoma bag was likely to be lower than both the company and ERG's preferred values, but higher than the utility derived by the company's elicitation study. It would have preferred to see analyses using alternative stoma bag disutilities. However, it concluded that, in the absence of alternative sources, the ERG's utility value should be used for decision making.*" As part of the vignette study the clinical expert explained and described problems that children may experience with a biliary stoma (Company response to clarification - Addendum C). This included problems with the area around the stoma becoming sore or infected. The bags were unpleasant and could leak, especially at night. The clinical expert noted that PEBD can have a significant impact on the quality of life for adolescents as they become more conscious of their bodies and start having relationships. The company identified two sources for the disutility associated with PEBD. The first was in patients with ulcerative colitis (UC) which gave a multiplier of 0.72 and the second in patients with colorectal cancer (CC), which gave a multiplier of 0.945. The UC study was selected as it was felt to be more analogous and relevant to PFIC than the CC study. Patients in the CC study were predominantly over 70 and the comparison made was patients with a stoma versus those with a major bowel resection, which is also expected to have a serious impact on quality of life. Other confounding factors were identified that may impact the multiplier, such as ongoing post-surgical complications and high rates of bowel dysfunction in the comparator group. On the other hand, patients in the UC study were younger and the comparison used to calculate the multiplier was ileostomy versus remission, which was judged to be more relevant to the application in the economic model. As described in the ECD, "*the clinical experts explained that the stoma-related effect on quality of life is significant, especially in older children. This is because the disutility may be larger in them and they often refuse an external biliary diversion. The clinical expert also highlighted that stoma-related quality of life was likely to be better for someone with colorectal cancer or ulcerative colitis than for someone with a stoma bag collecting bile. This is because of problems arising from the irritant nature of bile. The patient experts highlighted that people with PFIC and carers have a very negative attitude to having a stoma bag."* Albireo has further consulted with three clinical experts (see point 1) who confirmed that the disutility value derived from ulcerative colitis is appropriate but is still likely to underestimate the impact of a biliary stoma. Based on this feedback we believe that the committee's preferred disutility value based on the average of the colorectal cancer and ulcerative colitis studies (0.833) understates the impact of PEBD and that the true value would be closer to or worse than that for ulcerative colitis (0.722). As such, the company's base-case analyses assume a value of 0.722 for the utility multiplier associated

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	with PEBD. Further scenario analysis has been presented using the committee's preferred value (0.833) and the utility multiplier derived from the vignette study ('academic / commercial in confidence information removed'). See Appendix A.
4	**Response criteria and dose escalation** ***Criteria for dose escalation/definition of response*** In section 4.17 the ECD states that "*it had not been possible to determine a real-life definition of an adequate clinical response or specific criteria for dose escalation. The clinical experts classed an adequate response to odevixibat as improvements in at least 2 of the 3 main PFIC outcomes: serum bile acid levels, pruritus and liver function tests. They acknowledged that a definition of response might vary among clinicians. However, they explained that the dose of odevixibat would likely be increased if little or no improvement in these outcomes was seen*." Following the committee meeting Albireo has engaged with three clinical experts (see point 1) who have confirmed that the definition of an adequate clinical response stated in the ECD would be used in practice to determine the response and the need for dose escalation. ***Estimation of proportion of patients requiring dose escalation*** In section 4.20 the ECD states that "*The committee concluded that there was significant uncertainty surrounding the proportion of people having high-dose odevixibat and the serum bile acid response in these people."* It is difficult to predict with certainty the proportion of patients who will receive the higher dose of odevixibat. The definition of an adequate clinical response to be used in practice, as described above, is less stringent than that used in the clinical trials and economic model, where an sBA response was defined as a change from baseline to ≤70 µmol/L or a reduction of 70% after 72 weeks of treatment. Therefore, fewer patients are expected to require dose escalation than is currently estimated in the economic model based on sBA data from PEDFIC1, where 56.5% of patients did not achieve an sBA response to the lower dose (primary endpoint analysis).[12] In addition to the evidence already included in the company submission and provided during clarification, Albireo has discussed the topic of the proportion of patients that would be treated and remain on treatment on the 120mcg/kg/dose with the three clinical experts. Although there remains uncertainty on the proportion of patients who would be treated on the higher dose in clinical practice, the three clinical experts agreed that, based on the data available, it is reasonable to assume that [redacted] of patients would ultimately be treated at the higher dose. Albireo is also in discussions with NICE PASLU and NHS England to explore commercial options that may address and alleviate this issue. Please see point 7.
5	**PEBD as an option in the odevixibat arm** In section 4.22 the ECD states that "*It concluded that PEBD should have been included in both arms. It also concluded that the rates should be considered in exploratory analyses, if possible, informed by a data source that was clinically relevant to the NHS".* The NAPPED database in considered the most clinically relevant international data source for informing the rates of PEBD. It includes data from three specialist centres in England; however, no data documenting the rate of biliary diversion surgery in the UK were identified. In the SoC arm of the model when NAPPED data is used to inform the rate of PEBD surgery, 32% of patients undergo a PEBD and the company acknowledges that this figure may be too high. The rates of PEBD surgery in patients who have previously been treated with odevixibat are unknown; however, based

on clinical input this rate is expected to be much lower than in the SoC arm. During the committee meeting, one of the clinical experts stated that rates of PEBD in England are low and would be even lower after odevixibat.

In an advisory board attended by nine UK clinical experts, all experts agreed that the treatment pathway models for PFIC1 and PFIC2 proposed by Albireo for the company submission were representative of their practices.[13] The clinical experts concurred with the positioning of odevixibat in the treatment pathway and stated that they would not usually expect to use PEBD following odevixibat treatment.

However, NICE and the ERG received expert clinical advice that suggested that PEBD surgery could be offered to those who did not respond on odevixibat. We agree that in principle there is the potential for PEBD to be used after odevixibat; however, even if this were to happen it is expected to be at a much lower rate than in current clinical practice in the absence of odevixibat.

The company's updated base-case analysis follows the committee's preferences for modelling PEBD surgery. The rates from NAPPED are used in the base-case and PEBD is assumed to occur at the same rate in the non-responders to odevixibat as in the SoC arm. However, based on clinician advice that these rates may be higher than are seen in clinical practice, and that the rate among patients who have previously received odevixibat may be lower, the scenarios shown in the table below are also included. Crosses indicate a modelled scenario.

		Rate of PEBD in the SoC arm			
		Base-case	50% reduction	75% reduction	90% reduction
Rate of PEBD in the odevixibat arm	Base-case	X			
	50% reduction	X	X		
	75% reduction	X	X	X	
	90% reduction	X	X	X	X
	No PEBD	X	X	X	X

6

Rate of mortality after second transplant

During the committee meeting, it was raised that the mortality risk following a second transplant was higher than following a first. Watt et al 2010[14] explored risk factors for mortality post liver transplant and found retransplant to be associated with a higher risk of death beyond 1 year post-transplant. Patients that were retransplanted within 1 year had a mortality hazard ratio of 1.52 and patients retransplanted beyond 1 year had a hazard ratio of 4.79.

Scenarios have been included to explore higher rates of post-transplant mortality for patients that have been retransplated. In these scenarios, the probability of death beyond 1 post-transplant is weighted by proportion of patients that have undergone more than 1 transplant. The first scenario assumes all retransplants occur within 1 year and applies a hazard ratio of 1.52. The second assumes they all happen beyond year 1 and applies a hazard ratio of 4.79.

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7	**Options to address and alleviate the cost-effectiveness uncertainties** Albireo are in discussions with NICE PASLU and NHS England around commercial options that may further address the cost-effectiveness uncertainties. Albireo 'academic / commercial in confidence information removed'.
8	**Odevixibat is expected to have further impact outside of the NICE reference case** The company accepts that carer productivity costs are outside of the NICE reference case, however we maintain that these results reflect the important impact that odevixibat may have beyond the direct health benefits for patients and should be taken into account when appraising the cost-effectiveness of odevixibat. As evidenced by the results of the PICTURE study, 'academic / commercial in confidence information removed'. In the ECD carers explained that "*they needed to provide constant care to children with PFIC. Commonly, the demands are such that carers cannot work full time, resulting in loss of earnings and implications for career development. One carer explained that she could no longer carry on with her job as her daughter deteriorated because of the demands of juggling hospital visits and sleepless nights.*" A scenario analysis including these costs has been included.

Checklist for submitting comments

- Use this comment form and submit it as a Word document (not a PDF).
- Complete the disclosure about links with, or funding from, the tobacco industry.
- Combine all comments from your organisation into 1 response. We cannot accept more than 1 set of comments from each organisation.
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Odevixibat for treating progressive familial intrahepatic cholestasis [ID1570]

Appendix B: Updated base-case results with revised fixed price PAS

The revised updated base-case results with fixed price PAS reflect the committees preferred assumptions as outlined in section 4.34 of the ECD, with one exception. As outlined in comment 5, a utility multiplier of 0.72 has been applied for the PEBD health states. Table 1 presents the updated base-case results.

Table 1: Updated base-case results with revised fixed price PAS

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£) incremental (QALYs)
Standard care	[redacted]	20.89	[redacted]				
Odevixibat	[redacted]	22.91	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years

Table 2 presents the results of the scenarios considering different rates of PEBD, outlined in comment 4. Table 3 presents the results of the remaining scenario analyses.

Table 2: Scenario analyses considering different rates of PEBD with revised fixed price PAS

		Rate of PEBD in the SoC arm			
		Base-case	50% reduction	75% reduction	90% reduction
Rate of PEBD in the odevixibat arm	Base-case	[redacted]	-	-	-
	50% reduction	[redacted]	[redacted]	-	-
	75% reduction	[redacted]	[redacted]	[redacted]	-
	90% reduction	[redacted]	[redacted]	[redacted]	[redacted]
	No PEBD	[redacted]	[redacted]	[redacted]	[redacted]

Table 3: Additional scenario analyses with revised fixed price PAS

Scenario	Inc. costs	Inc. QALYs	ICER
Base-case	[redacted]	[redacted]	[redacted]
Committees preferred analysis (stoma utility multiplier = 0.833)	[redacted]	[redacted]	[redacted]
Stoma multiplier from the vignette study ([redacted])	[redacted]	[redacted]	[redacted]
Carer productivity costs included	[redacted]	[redacted]	[redacted]
HR of 1.52 applied to post-LT mortality	[redacted]	[redacted]	[redacted]
HR of 4.79 applied to post-LT mortality	[redacted]	[redacted]	[redacted]

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Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	**Children's Liver Disease Foundation**
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	**N/A**
Name of commentator person completing form:	[redacted]

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Example 1	We are concerned that this recommendation may imply that ……..
1	**Unmet need and no other treatment options available:** This is an unmet need with no alternative, comparative, non-surgical treatment available specifically for PFIC. Off label treatments may support with aspects such as pruritus and vitamins and dietetic services can support with nutrition but with varying degrees of success. Many rely on practical solutions unless/until it reaches the point of liver transplantation which carries a high level of risk. While there are other treatments being trialled in this cohort of patients this is the only drug in the pipeline for PFIC patients in the near future.
2	**There was agreement that it has an impact beyond direct health benefits. However, we have provided some comments below regarding the committee responses to this area:** Surgeries (transplant and biliary diversion) have greater impact on the whole family in a variety of ways. There are not only financial implications but mental health and psychological impact on the child as well as the parents and siblings also need to be considered. Furthermore, there will be greater time spent away from other children/siblings/partners in these circumstances which increases anxieties and effects relationships. This drug may reduce the number of visits necessary because of a potential reduction in pruritus, its effects, and the need to manage these. Of course, they will still need to attend appointments to monitor the condition but the number of visits outside of follow up and general management appointments could potentially be reduced. Delay the time to transplant – liver transplant may be needed at some stage but there are benefits to attempting to delay this and keep the child's native liver as long as possible. It may reduce the need to be on immunosuppressants until as late as possible and the associated effects. The risks of surgery are great as well as the increased risk of infections and viruses due to immunosuppressants and risk of cancer (PTLD). Transplantation also reduces the sports and social activities they can get involved in (e.g. contact sports) and careers they can undertake (roles that involve increased exposure to infections and/or heavy lifting/contact). Transplant although lifesaving is not a cure, those patients need a lifetime of care. The ongoing immunosuppression not only has its own risks in the longer term, the child and family live with the ongoing concern that the new liver may fail at some stage leading to the need for further lifesaving transplants. The goal for most families and professionals is for a child to live with their native liver for as long as possible.
3	**Uncertainties:** Uncertainty is a characteristic of rare diseases, in particular a complex organ such as liver, but even more complex in children compared to adults. How each patient is impacted and to what extent varies considerably. Regarding some of the uncertainties raised in the ECD, it would require paediatric hepatology services restructure in terms of databases, policy and processes and much increased levels of research to overcome some of these which will take many years due to the little resource this field has in terms of specialists, researchers and patient numbers.

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	In relation to other subgroups, PFIC 1 and 2 are the most common in children and form the majority of PFIC diagnoses. Therefore, according to the committee recommendations, the majority will lose out because of insufficient evidence for much rarer sub-groups where recruiting patients will be considerably more difficult.
4	**Final overview:** This is an unmet need with no alternative comparative non-surgical treatment available specifically for PFIC. Uncertainties are common in research and trials with rare disease patients particularly children with small cohorts of patient groups in a variety of subgroups. The overall assessment of NICE in terms of clinical effectiveness was that, in the time of trial, it had positive outcomes for a number of patients in that it was effective in reducing both serum bile acids and pruritus in both PFIC 1 and 2. This seems to indicate it is clinically effective. By not approving this technology the benefits patients could gain in the short term are being obstructed due to lack of long-term data which will take many years. There is an urgency for treatment now with no other drugs in the pipeline for this condition. There is currently no other treatment available for these patients so any benefit they could gain (short/long term) from being prescribed this medication as a step before transplant to be able to manage symptoms and side effects would be advantageous to not only the child but their whole family. Quality of life would be considerably improved with the potential to reduce serum bile acid levels and pruritus. Below comment from PFIC family: “I looked after my grandson on a few occasions in the early days after his diagnosis with this disease. It was heart breaking to watch him always crying and covered in blood from scratching his skin off. He could not participate in any normal childhood activities and was either crying or sleeping. The medication trial was then offered to him and within months the improvement in his health and quality of life was incredible he became a different child and to any who did not know his story he was a normal healthy child.”
5	
6	

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Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	Birmingham Women' & Children's Hospital
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	[No links to tobacco industry. Previous conflicts have been declared with Pharmaceutical Industry. No new conflicts
Name of commentator person completing form:	Professor Deirdre Kelly

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1	Page 3. There are few data on treatment with or without Odevixabat in other types of PFIC because it is a rare disease and Types 1 & 2 are the most common. It would be impossible to carry out clinical trials and add to the data on other types of PFIC
2	Page 7 Agree the effect of Odevixabat on QoI in affected patients and families is significant & there is unmet need
3	Page 9 - 4.5. Agree pathway of care is determined by type of PFIC, but Odevixabat may improve QoL, pruritus and liver function in any of the types evaluated
4	Page 9 – 4.6 SBD is not standard of care in UK and is only an alternative to PFIC 1 because the disease is not curable with Tx and S/E post-transplant (diarrhoea etc) are debilitating. If no response to Odevixabat, then SBD is unlikely to work. Off label medications are current standard of care
5	Page 14 – 4.12 There are few data on treatment with or without Odevixabat in other types of PFIC because it is a rare disease and Types 1 & 2 are the most common. It would be impossible to carry out clinical trials and add to the data on other types of PFIC
6	Page 17 -4.17. It is difficult to make a recommendation on dose escalation in view of the design of the studies. In practice, patients would start on the lower dose and the dose would only be escalated if there was an insufficient response using the parameters agreed in 3 months. It is likely that only 30% patients of need the highest dose.
7	Page 19 – 4.19. I do not agree that SBD should be included as an option in the treatment arm as If no response to Odevixabat, then SBD is unlikely to work
8	Page 25 – 4.31. Difficult to apply standard QALYs developed in adults to infants with a rare disease

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Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	[**Insert disclosure here**]
Name of commentator person completing form:	[Richard John Thompson, ,Professor of Molecular Hepatology at King's College London, and Honorary Consultant Paediatric Hepatologist at King's College Hospital, London]

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1	I believe that the similarity of the mechanism of action of odevixibat and SBD have been underestimated. I believe that has had effects on the modelling. Both forms of treatment seek to interrupt the enterohepatic circulation of bile acids, after export from the liver. The purpose of this measure if to reduce the bile salt pool size, and critically to reduce the requirement for the liver to transport bile acids. If this requirement is reduced to a level below the capacity of the liver to transport bile acids then the primary problem has been overcome. This concept applies to all forms of PFIC identified so far, except MDR3 and FXR deficiencies. The latter is not expected to respond, however the former is biologically an excellent candidate, although there is no intrinsic problem with bile salt transport. Instead the problem is of damage to the liver by effectively transported bile acids. Reduction in bile salt flux through the liver, in MDR3 deficiency, will reduce the concentrations of bile salts in bile, and therefore reduce the damage. MDR3 is quite different in this respect from the other forms of PFIC in this respect.
2	Because the mechanism of action of odevixibat is so close to the intention of SBD I believe the modelling does need some further thought. Both forms of treatment have the potential to radically transform the natural history of PFIC and completely remove the need for transplantation, in those patients where the treatment is successful. Following on from the above, the intended reduction in the requirement for bile acid transport, will prevent the accumulation of bile acids in the liver, prevent progressive liver damage, significantly reduce the pruritus and as a secondary consequence reduce serum bile acid levels in peripheral blood. Please note that it is bile acid levels in the liver that are damaging, and almost certainly lead to pruritus. Peripheral blood levels are an indirect, although clinically available, measure.
3	The NAPPED studies, of which the committee are very aware, are critical in showing that reduction in serum bile acids (although an indirect marker), after interruption of the enterohepatic circulation of bile acids, are predictive of transplant avoidance in both FIC1 and BSEP deficiencies. As the committee noted, SBD is not an ideal treatment for many reasons. Not only is it disfiguring and psychologically problematic, it also predisposes to electrolyte disturbance and cholangitis. The proportion of bile acids diverted is always very unclear.
4	I believe that SBD should be used as a comparator in the modelling.
5	I believe that the NAPPED data indicate that effective depletion of bile acids dramatically changes the natural history of these diseases.
6	I have looked after a lot of patients with PFIC. It is a devastating disease. The pruritus destroys patient's and families' lives. Liver transplant is a very good treatment for BSEP deficiency. But has considerable short and long term risk, as noted by the committee. It is not a good treatment for FIC1 deficiency, as it frequently makes the gastrointestinal symptoms worse. However the fact that families are very prepared to put their children's lives at considerable risk (by subjecting them to transplantation) in order to overcome the pruritus, tells you everything you need to know about the awfulness of this symptom, in this disease.
7	I think that I understand the constraints of the NICE modelling, though it is far from my area of expertise. Somehow the process seems to have underestimated the life changing effect that this treatment has had on both children with PFIC and their families.

Insert extra rows as needed

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Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	[**Insert disclosure here**]
Name of commentator person completing form:	Claire Brinkley

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1	As a parent of a PFIC child, I cannot express strongly enough how much of a difference this drug would make. Transplant is not an acceptable treatment for children. It is unbelievably traumatic and not a cure. The impact of the itch on the child's quality of life is huge. It feels akin to physical abuse to allow a child to suffer in this way, scream through the night and rip their skin until it bleeds, then unable to learn in school as a result, when there is a medication that could prevent all of this.

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Note: We reserve the right to summarise and edit comments received during consultations, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received during our consultations 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 comments we received, and are not endorsed by NICE, its officers or advisory committees.

Please return to: **NICE DOCS**

Comments on the ECD received from the public through the NICE Website

Name	[redacted]
Role	Carer
Other role	
Organisation	
Location	
Conflict	
Notes	
Comments on the ACD:	
[redacted] my daughter has been on this medication for nearly 2 years and it has changed her life dramatically. She still lives daily with a itch but it is much more bearable. It had improved get energy levels, her blood results, her sleep and had a massive impact on improving her quality of life. Just because this disease is rare it does not make medication like this any less important whatever the cost may be. I strongly feel this should be recommended by NICE for PFIC patients but also for other liver conditions that it may have some beneficial potential	

Name	[redacted]
Role	Carer
Other role	
Organisation	
Location	
Conflict	
Notes	
Comments on the ACD:	
I am disappointed to learn that NICE is not recommending Odevixibat at this time. Our doctor has said our 4 year old who has been diagnosed with an undefined type of PFIC would be a good candidate for this drug. Currently, her treatment options are very limited and we have been anxiously waiting for the time when we might be able to give her something to help with her quality of life. Though her liver is functioning relatively well clinically speaking, her itch makes sleeping and concentrating at preschool difficult. We have good insurance through my husband's work but they are still reviewing whether or not to approve this new treatment and recommendations like this are so important. I understand that there are equity issues associated with the cost and potential limited effectiveness in rarer types of PFIC but these kids deserve a chance at a normal life and it's within your power to help them have that chance. If this medicine helps helps even a small percentage of kids it would be worth it.	

Name	[redacted]
Role	Public
Other role	
Organisation	
Location	
Conflict	
Notes	
Comments on the ACD:	
This drug needs to be available for children like [redacted]. This drug has made a tremendous difference to her quality of life. It has reduced her suffering massively. she has been allowed to enjoy her childhood as a 4 year old. This drug helped	

reduce hospital visits and aided her parents being able to manage her disease. Please give [redacted] the opportunity for life like we all deserve.

Name	[redacted]
Role	Public
Other role	
Organisation	
Location	
Conflict	
Notes	
Comments on the ACD:	
This is extremely beneficial and needs to be passed. This has helped and made such an impact to a little girls quality of life. This has had such a huge impact on her ,to take away would be to deny the good work this had done. This is so imperitive, you can only see the results when you see them for yourselves.	

Name	[redacted]
Role	Public
Other role	
Organisation	
Location	
Conflict	
Notes	
Comments on the ACD:	
I have seen how much of an impact this medication has had on one little girl. It would be devastating for her not to receive this anymore. Life changing.	

Name	[redacted]
Role	Carer
Other role	
Organisation	
Location	
Conflict	
Notes	
Comments on the ACD:	
As a parent of a PFIC child, I am saddened and disheartened by this decision. There were no options for a drug intervention when my child needed it and we ended up in the difficult situation of proceeding with a liver transplant at only 18 months old. As a result of the PFIC, my child suffered a brain bleed, failure to thrive, rickets, a broken arm, severe gross motor delays, feeding intolerance, multiple surgeries, and my having to leave my job to be a full time care taker. The thought that this drug is “too expensive” is absolutely disgusting. If this drug had been available when we needed it our lives could’ve been drastically different. The patient needs to be the focus of the benefit of this drug rather than the cost being the reason it is not approved.	

Name	[redacted]
Role	Carer
Other role	
Organisation	
Location	
Conflict	
Notes	

Comments on the ACD:
I'm member of family with child with PFIC2 and physician. Please accept medicine odevixibat (Bylvay) in UK. If my niece does not get the medicine, her life and our family life will be miserable and sensless. Sorry for my English. I do not life in the UK.

Name	[redacted]
Role	Public
Other role	
Organisation	
Location	
Conflict	
Notes	
Comments on the ACD:	
I read the report with interest after I met a child with this condition. The report is frustrating as it appears that part is the issue is that the study has such a small sample. It is difficult as I have witnessed the positive impact on the child over the last few months (I commented on this just a few days ago) and am Aware of the significant improvement in her health. This in turn has increased her confidence and social interaction.	

Name	[redacted]
Role	Public
Other role	
Organisation	
Location	
Conflict	
Notes	
Comments on the ACD:	
I have seen first hand what an amazing difference this drug has made to my friends daughters quality of life. Without this drug her life would digress dramatically!	

Name	[redacted]
Role	Pfic Italia Network president
Other role	
Organisation	Pfic Italia Network
Location	
Conflict	
Notes	
Comments on the ACD:	
"As Organization and community here in Italy, we want to bring our expirience. This medicine it's been a life change for a lot of our family. Living with itching is not life. Please your decision will be very important for all the world. Thank you Pfic Italia Network "	

Name	[redacted]
Role	
Other role	

Organisation	
Location	
Conflict	
Notes	
Comments on the ACD:	
"I am a mother of a three-year-old child with pfic 2. Albireo's drug changed our life. The symptoms of the disease are now under control. My son is fine, happy and has a life like all other children. Everything is fine thanks to Albireo's drug."	

Name	[redacted]
Role	Carer
Other role	
Organisation	
Location	
Conflict	
Notes	
Comments on the ACD:	
Odevixibat is the only symptom relieving medication currently in use for patients with PFIC1. My granddaughter has benefitted tremendously during the clinical trials using this drug with very few side effects. Her sleep pattern has dramatically improved due to a reduction in itching. Currently she will need to stay on thr trial with regular blood tests etc which are distressing for her. Approval for funding this drug definitively would negate the need for continual monitoring. I cannot stress strongly enough how much this drug has enhanced my granddaughters quality of life	

Name	[redacted]
Role	Carer
Other role	
Organisation	
Location	
Conflict	
Notes	
Comments on the ACD:	
Without this drug my granddaughter would have even greater difficulty sleeping. She has started school and sleep is essential. It therefore is essential for her quality of life. She has been on the trial which although grateful for the drug it has mesnt monthly monitoring including blood tests. This little girl has many drugs and injections to cope with without the extra discomfort of this monitoring. It now involves missing schooling. It is difficult to express how much difference this drug has made to [redacted] life.	

Name	[redacted]
Role	Carer
Other role	
Organisation	
Location	
Conflict	
Notes	
Comments on the ACD:	

As a mother of a child with PFIC, this drug is groundbreaking and will literally save and change lives of children all around the world. We have seen the dramatic impact it has made in our PFIC community for our children. There is no expense too high to save children's lives. This also gives our children's the chance of a transplant free life and to give the transplant livers to other children that don't have these life changing drugs yet. Please please please know that this drug is a miracle and we have hundreds of us that would back that up.

Name	[redacted]
Role	NHS Professional
Other role	
Organisation	
Location	
Conflict	
Notes	

Comments on the ACD:

"

Re: Odevixibat for treating progressive familial intrahepatic cholestasis [ID1570]

Dear Sir/Madam,

I'm writing to give personal experience about the effects of PFIC which I have witnessed as godmother to a one year old girl who has the illness, and to strongly request that odevixibat is approved in the UK, as it has been in the USA and EU already.

I have had to watch my best friend (the mother of the little girl) suffer through what has undoubtedly been the worst year of her life. Having hope built up when the FDA approved the drug to it being crushed following this initial consultation from NICE has been soul destroying to day the least.

Shortly after the birth, my goddaughter was diagnosed with the umbrella term of failure to thrive. It took 7 months to determine the cause, which likely would have taken a lot longer had it not been for her parents relentless efforts to research themselves and fight tooth and nail for answers. All through a pandemic. Their daughter endured seven months of consistent vomiting, diarrhoea, nutrient deficiencies, inability to sleep, stunted growth, consistently deranged and worsening liver function test results. Both parents have become incredibly exhausted, to the point that the 31 year old father now has severe cardiac problems, resulting in inability to work or look after his baby as usual; the 30 year old mother is underweight, has fallen multiple times due to sleep deprivation and exhaustion, she is due to go back to work following maternity leave but may be unable due to her daughter's specialist needs. Not to mention the devastating impact to their mental health, both now have depression and anxiety issues not only due to the worry around their daughter's illness but also now financial strains which are a direct result of PFIC. I feel scared for their health as individuals, on top of the risks PFIC imposes on my goddaughter, the three of them have been in and out of multiple hospitals all year and it doesn't look like that is about to change.

Odevixibat will go much further than symptom management for families impacted by the effects of PFIC. Although mentioned, I do not believe this has been adequately considered in the consultation. It impacts the wider economy, through parents struggling to work, as well as the right to equal education of the children effected who will struggle to attend school.

I hope NICE consider these personal experiences as well as the wider picture and approve odevixibat for use in the UK. It will likely improve my goddaughter's quality of life in so many ways, as well as her parents, and hopefully delay the progression of PFIC ultimately extending her life expectancy.

Yours sincerely,

[redacted]

In the time it's taken me to write this her parents have had to call 111 who have advised an ambulance, for what feels like the millionth time in her short life so far. It's relentless, please help them and others."

Name	[redacted]
Role	Public
Other role	
Organisation	
Location	
Conflict	
Notes	
Comments on the ACD:	
This treatment has given a little girl I know a normal life, she has gone from being a frail little thing to a vibrant healthy and miracle girl! It's hard to believe how far she has come!! Without this treatment she wouldn't have been able to live like she does and struggled tremendously. The results speaks for itself it's an incredible transformation, she has just started school and loving every minute it's wonderful to see. I hope that the information is reviewed and considered, this treatment changes lives so much for the better!!	

Name	[redacted]
Role	Public
Other role	
Organisation	
Location	
Conflict	
Notes	
Comments on the ACD:	
I have seen the effect this drug has on the life of children and feel it should be approved.	

Name	[redacted]
Role	Public
Other role	
Organisation	
Location	
Conflict	
Notes	
Comments on the ACD:	
"It is the first and as yet only treatment that has ever got this far towards approval for children with PFIC. There are not many others and they are all still in the trial stages. It has helped patients with pruritus but also growth, blood results and health in general which has had a knock on effect with speach, confidence and general quality of life. Especially because it is a rare disease patients should deserve the opportunity to treatment and quality of life. "	

Name	[redacted]
Role	Public
Other role	
Organisation	
Location	
Conflict	
Notes	
Comments on the ACD:	
This medication has changed someone I know little girls quality of life massively. Please approve this medication	

Name	[redacted]
Role	Relative
Other role	
Organisation	
Location	
Conflict	
Notes	
Comments on the ACD:	
It is essential that this drug be made readily available to ensure the ongoing quality of life for all young children suffering from PFIC. Without sleep from constant scratching it not only affects the sufferer but every member of their family too. Please ensure this drug is made available.	

Name	[redacted]
Role	Carer
Other role	
Organisation	Children's Liver Disease Foundation
Location	
Conflict	
Notes	
Comments on the ACD:	
As a carer of a child with liver disease these new medicines and vital to help our children. To increase the help of their condition, quality of life, slow down or stop transplant, making living life with liver disease more manageable, these new drugs are vital and must be approved ASAP.	

Name	[redacted]
Role	Carer
Other role	
Organisation	
Location	
Conflict	
Notes	
Comments on the ACD:	
"With a continually ageing and obese population, the demand in future for liver transplants is bound to increase. The treatment of PFIC at an early stage will help to reduce cholestasis, resulting liver damage and ultimately the demand for liver transplants. As a parent of a young person who went through a liver transplant I have first hand knowledge of the distress and agony a transplant puts on a patient and their family. Though there is a cost figure which can be placed on the transplant itself, who	

knows the cost of this stress on a child's parents too? If this can be avoided in any way, I would support this.
The amount of school days missed through ill health and treatment leading up to and during a transplant has an enormous impact on the young persons education, mental well being and life chances. So, anything that can be done to avoid the need for a transplant has to be worthwhile.
While I accept the cost of this drug is expensive, I understand the condition is very rare so the number of claims for this medication is likely to be quite small. As well as considering the savings from not needing a transplant, and all the support costs around that, please factor in additional costs associated with subsequent mental health. My daughter has experienced a number of mental health issues since missing out on so much social interaction with her peers through needing a transplant. She has needed costly support from CAMHS on a number of occasions.
For these reasons, please reconsider approval of odevixibat."

Name	[redacted]
Role	Carer
Other role	
Organisation	
Location	
Conflict	
Notes	
Comments on the ACD:	
Our 14 year old son, [redacted], has been taking Odevixibat as part of an extended trial since May 2019. Since then, we have seen a dramatic reduction in the itching that comes with his PFIC2 diagnosis. He can now sleep through the night for almost the first time in his life. Prior to starting the medication, he was so massively sleep deprived and itchy that we considered taking him out of school. We thought we were heading towards an inevitable transplant due to intolerable pruritus. [redacted] could not concentrate on his schoolwork and often needed to have a nap in the middle of the day. His itching particularly affected his legs and feet and these were always scabbed, scarred and bloody. Every night, he would get blood on his sheets. The whole family suffered from sleep deprivation along with [redacted]. He was not able to sleep in a room on his own. He can do this now. The scars on his legs have started to fade. The whole family is more rested. [redacted] can now concentrate more effectively on his schoolwork and enjoy his leisure time without the constant need to itch. He has a more positive outlook and so do we! We couldn't imagine doing without the medication now. No other treatment is available that effectively addresses [redacted] pruritus. Without it, his educational and mental health outlook would be very bleak. The essential visits to hospital and to mental health professionals were much more frequent before starting on Odevixibat. In short, it has saved our son and our family from a most dismal future and greatly reduces the prospect of overutilizing our national health resources.	

Name	[redacted]
Role	Carer
Other role	
Organisation	
Location	
Conflict	
Notes	
Comments on the ACD:	

I am the mum of a child who has been on this medication for almost 2 years now.. The impact it has had on her life and the whole family's life has been phenomenal. The medication has helped with her pruritus meaning better sleep, better concentration and less scarring. This helps [redacted] both with her physical health but also get mental health. People always used to comment on all get scratch marks which she was starting to pick up on. This has stopped now. This has also had an impact for the better in the whole family as she doesn't wake her big brother up and myself and get dad have to get up less throughout the night which has a huge impact on how we can cope and manage each day. Not only has it helped her pruritus it has completely stabilised her disease progression. Since being on the medication her blood have stabilised, her liver and spleen size had stabilised and she has so much more energy. In fact I would go as far as to say she is like a different child. It has also improved get growth which in turn has helped with her development. I cannot express how much I am an advocate for this medication and how it has completely stabilised this cruel condition for my daughter. She has now been able to start school and is keeping up with her peers. Something I never thought we would see. I really hope you see the benefits as I do and see how much this could help other children, slowing the progression and ultimately reducing the need for invasive treatment and transplants which would be a lot more costly in the long run.

Name	[redacted]
Role	Carer
Other role	
Organisation	
Location	
Conflict	
Notes	
Comments on the ACD:	
Our teenage son has been on Odevixibat for several years now to reduce itchiness brought on by his PFIC TYPE 2 condition. The medication has been life changing for him. He used not to be able to sleep due to scratching all night. This caused both tiredness and inability to concentrate at school (along with his itchiness) taking many years of education off him. He was tracking 3-5 years behind his peers. Since being put on the medication, he is still itchy, but to nowhere near the extent previously. He is catching up, and can concentrate during school. It seems to have also arrested the progressive deterioration of his liver. We are resigned to having daily medication into the distant future. However, we would much rather have medication supporting his own liver, than other medication stopping his body rejecting a foreign one.	

Name	[redacted]
Role	Carer
Other role	
Organisation	
Location	
Conflict	
Notes	
Comments on the ACD:	
"My comments that follow are direct from me as a mother of an infant with a rare liver disease (Alagille Syndrome) who experienced severe pruritus from the age of approx 4 months with increasing severity up until the point of liver transplantation at 17 months old.	

I understand that children diagnosed with PFIC also suffer with extensive itching due to pruritus.

Pruritus affects the patient 24 hours a day, it is not forgiving of what you are doing, if you need to rest or if you need to concentrate for a moment (such as simply concentrating on bottle feeding in an infant).

My son was not only continually unbearably itchy (think a thousand ants crawling over your body and not being able to get to them). But he would subsequently cut his skin open and bleed. His liver disease caused his blood to not clot properly, so the bleeding was hard to stop.

Something as simple as getting in the bath would trigger his itching even more. An enjoyable experience for a baby, taken away by the pain of discomfort.

Bedtime was always an issue as as he tired, the itching would worsen and keep him from peacefully drifting off to sleep. He would wake in the night cutting his skin open.

As the parent / caregiver there was not let up. Woken every night like we had a newborn as his sleep was so disturbed due to the itching.

Memories of soothing your baby to sleep by stroking their soft skin never made as you simple comforting them would encourage their desire to scratch themselves.

Continually dressing your child in vests, long sleeves, socks, mittens to try and preserve their beautiful, delicate skin from being cut open and scarring.

Odevixibat would enable patients to go about their daily lives in the way the majority of us take for granted - mainly being able to concentrate at school or work and not be fatigued by the lack of sleep from itching. It would in turn enable the parents / caregivers to do the same.

The monotonous condition, if studied correctly, would no doubt show an increase in depression and anxiety in both the patient and caregiver over time which in turn would also be costly to the NHS.

The longer term would see less absences from school and work and hospital visits, again keeping the mental health of the patient and parent / caregiver stable.

Pruritus is one of the most debilitating parts of liver disease as it is constant and unforgiving. And let's remember that this is generally only one symptom of liver disease as a whole, with many patients also suffering with fat absorption issues, vitamin absorption issues (in turn growth issues) constant blood work, hospital visits, other medication etc.

Please consider how much this medicine could potentially save someone's quality of life, even if they only are able to survive for a short while, at least they would be comfortable. "

Name	[redacted]
Role	Public
Other role	

Organisation	
Location	
Conflict	
Notes	
Comments on the ACD:	
This drug has had a huge impact on the quality of life of my niece. She is able to sleep more at night as a result. Not proving this drug will be a huge detriment to the quality of life of those suffering from these conditions. I believe this has not properly been taken into consideration.	

Name	[redacted]
Role	Carer
Other role	
Organisation	
Location	
Conflict	
Notes	
Comments on the ACD:	

"Re: Grandmother of patient with PFIC and the authorisation of Odevixibat

My darling little granddaughter E has been diagnosed with PFIC. It has been a tough time. She nearly died; following a traumatic birth E lost so much of her body mass she was on the 0 percentile for baby weight and the term failure to thrive was used. Covid did not help matters. Her parents; S (my daughter) and J have struggled to get a diagnosis, and have endured months of sleepless nights, living with a baby in pain, the anxiety of not knowing why their child is so poorly, being unable to fix or resolve E's illness.

Despite restrictions and at great cost I have travelled form Spain to the UK to help this little family when they were on theirs knees with exhaustion. J trying to work extra night shifts and long hours with the burden of a seriously il child has caused life threatening problems with his heart, he himself been in hospital for over a week in all. S has lost an excessive amount of weight; she has persevered with breast feeding to help E gain as much weight as she can. Working tirelessly with the dieticians S has, through trial and error, found a diet to suit E. Now S is going back to work, the burden of a sick partner and sick child she will have to carry as she works for her wildlife charity.

How much does a liver transplant cost?? Not just in the operation but the anti-rejection drugs, the trauma to the family unit, the life expectancy and quality of life for the patient before and after. I cannot stress enough how much little [redacted] needs this drug. Not only so that she can reach her full potential in life, but for the sake of the NHS so she avoids the prospect of a hugely costly liver transplant, and to avoid the deterioration of her health as E grows. E can lead a strong normal healthy life, with the authorisation of this drug. Moreover, so her parents can recover and provide economically and emotionally for her. So that they can all play their role in the bigger community.

As a teacher working in secondary schools for over 20 years in the UK I know how difficult life can be for children with learning difficulties. It is the cost for the school when resources are tight, for other pupils, for the parents, for the child. By permitting the use of this drug E can grow and develop to her full potential without the fear of a liver transplant and the loss of education that that will entail.

My daughter S has been poorly with gall bladder issues that remained undiagnosed from the age of 15. She eventually (6 years later) had her gall bladder removed at 21, after a junior doctor in A and E made the right diagnosis. S had to wait 38 weeks before her gall bladder was operated on by which time, she

could only eat boiled vegetables and water. [redacted] had to take a year out of university because of this illness. During her pregnancy there were no considerations made about her previous medical history and S had a traumatic difficult birth induced at 36.5 weeks when the baby started to be affected by [redacted] cholestasis. Action has taken to combat this disease. Please consider this letter and its contents in your decision to approve Odevixibat for use in the UK.
Thank you for reading this letter and considering the case of [redacted] and all other people suffering because of this terrible disease.

Name	[redacted]
Role	Public
Other role	
Organisation	
Location	
Conflict	
Notes	
Comments on the ACD:	
It would be amazing if this treatment was approved to assist my lovely great niece to have the wonderful long and fulfilled quality of life that she deserves.	

Name	[redacted]
Role	Public
Other role	
Organisation	
Location	
Conflict	
Notes	
Comments on the ACD:	
"[redacted] a current PFIC patient urgently requires this treatment to ensure her quality of life and that of her devoted parents is sustainable. I have witnessed their turmoil over the first year of her life and it has been harrowing. The constant anxiety waiting for results, a diagnosis and endless hospital admissions. The pressure and strain this has put the whole family under has been immense. This drug has provided some relief, light in a dark time and hope of a better future for them all. I emplore you to consider providing [redacted] with this treatment she so desperately needs. She has her whole life ahead of her, dreams to fulfil that she doesn't yet know of and a life which will forever be supported by her parents."	

Name	[redacted]
Role	Public
Other role	
Organisation	
Location	
Conflict	
Notes	
Comments on the ACD:	
This drug will really benefit the health of so many. I look forward to seeing it being used	

Name	[redacted]

Role	Carer
Other role	
Organisation	
Location	
Conflict	
Notes	

Comments on the ACD:

"Consultation on the use of Odevixibat for treating Progressive Familial Intrapahetic Cholestasis (PFIC)

Dear Sir/Madam,
I am responding to your consultation on the use of Odevixibat as a concerned parent of a child [redacted] with PFIC, type 3 MDR3+ deficiency. I feel compelled to respond on hearing that NICE has decided not to recommend the reimbursement of Odevixibat which is a treatment for this illness.
Comments on the consultation
It is clear the side effects of Odevixibat are mild/moderate and well managed by patients however this has not been given sufficient weight when compared with PEBD and other very limited treatment options. Improved symptoms and limited side effects also equal less clinical intervention and use of NHS resources as patients inevitably worsen or require surgery without the drug. The benefit of non-intervention has also been understated. This is especially when Odevixibat requires no further safety monitoring and can be administered easily and non-invasively. It could also be administered locally under supervision in appropriate cases. The invasive nature of other treatments have been understated when considering utility. There are no alternatives that are non-invasive and have few side effects. This has not been given sufficient weight in the committee's analysis. Transplants are associated with long surgery, hospital stays, risks of complications and risk of infections as well as continued medical intervention and medicine for life. The role of Odevixibat in preventing transplant for as long as possible and the benefit of this has not been given sufficient weight. Carers disutility was not given enough analysis. It is appreciated the committee felt this was uncertain however significant evidence was provided about the significant impact PFIC has on carers and the level of care PFIC children require, especially considering the overwhelming impact on sleep. This impact has been understated when considering the other improvements to quality of life of families other than physical health. The benefits are psychological, educational and financial.
The committee should consider postponing a final decision until the indirect comparison between Odevixibat and PEBD and SBD has been completed by the company. The committee recognizes the importance of this assessment and that many of the uncertainties that led to the decision not to fund Odevixibat could be resolved by more data collection. If that is the case, given the lack of treatment options and the clear evidence of the impact on patients, the committee should reconsider its rejection of a managed access agreement to obtain further data. The failure to apply any additional QALY is very harsh based on the data and means that Odevixibat was doomed to fail to the extent that consideration for a managed access agreement would not be considered. I feel this is unfair and should be reconsidered to at least provide the opportunity to explore these issues further. It the committee is not minded to agree, the review date should be linked to data collection rather than 3 years.
Personal experience of PFIC
My daughter [redacted] is 12 months of age and has had a challenging start to life. At 10 days old she was admitted to hospital with failure to thrive, significant weight loss and spent much of the first 3 months of her life in hospital appointments and

being subjected to numerous tests. Often these tests involved painful procedures and fasting when her illness meant she was already starving and dehydrated. She had almost constant extreme sickness and diarrhea as well as highly elevated liver enzymes. The knock-on effect of this was that she did not gain weight or obtain the nutrients she needed and had stunted growth with a disproportionate head to body ratio. This illness is rare and it has been a significant challenge trying to get the right diagnosis. I have needed to advocate for her and push for specialists to conduct genetic testing to co"

Name	[redacted]
Role	Public
Other role	
Organisation	
Location	
Conflict	
Notes	
Comments on the ACD:	
[redacted] and other children need this medication to better her life. This medication is needed	

Name	[redacted]
Role	
Other role	
Organisation	
Location	
Conflict	
Notes	
Comments on the ACD:	
My friend [redacted] baby - [redacted] - needs this medication. She is a beautiful baby girl, whose mum and dad are worried sick about what the future holds. Offering this medication would give them hope and reassurance for the future. Please consider those for who a liver transplant would not be successful.	

Name	[redacted]
Role	NHS Professional
Other role	
Organisation	
Location	
Conflict	
Notes	
Comments on the ACD:	
"Odevixibat has been approved in both the USA and EU to help treat PFIC, delaying the need for liver transplant and increasing life expectancy. It also improves growth which can often be stunted without treatment, as well as improving horrendous symptoms such as pruritus (extreme itching) which is otherwise debilitating, constant and unrelievable. Imagine itching all over your body, from the inside out, and no amount of scratching makes it better. But Odevixibat can. The itch causes sleep deprivation, impacting the wider family as well as the child's development and ability to attend school. Why should babies and young children in the UK suffer, knowing there is a drug out there which can help? It is not right."	

Name	[redacted]
Role	Carer
Other role	
Organisation	
Location	
Conflict	
Notes	
Comments on the ACD:	
"I have seen first-hand the devastating effects of Progressive Familial Intrapahetic Cholestasis. During the first three months of my daughter's life [redacted] was hospitalised for 75% of this time, when she should have been at home with her family. To make matters worse this was during the Covid-19 pandemic, when only one parent could be with their child. I was completely useless and could not help her or her mother to care for her. The separation made it incredibly difficult to develop the initial bond with my daughter, which I feel would have been present immediately if she had not been so ill. I had to watch her suffer for many months, with no idea what the prognosis would be. During this time she became very malnourished and suffered from failure to thrive. This is not something I would wish on my worst enemy. As a family we have suffered from extreme sleep deprivation which in turn has affected the quality of our lives and our ability to carry out our normal work duties, putting further strain on our lives due to loss of income. This coupled with the increased cost of the specialist foods she requires, due to digestive problems has compounded the strain further. The effects of this disease are incredibly distressing, particularly as there are no low risk or non-surgical treatment options. I do not wish to see my daughter growing whilst knowing the bleak outlook for her condition, when there is something out there that could change her life for the better. I urge you to reconsider your decision to allow children and their families to have a decent quality of life, education and future."	

Name	[redacted]
Role	Family member
Other role	
Organisation	
Location	
Conflict	
Notes	
Comments on the ACD:	
"My Granddaughter has this condition,it has had a dramatic effect on the entire family.If she could receive this drug it would greatly improve the mental and physical health of the entire family,as well as reducing the very likely need for a liver transplant .Surely this cost along with all other costs must be considered prior to any final decision. In my life I had to witness many horrific sites,but nothing has prepared me for this ,my daughter and granddaughter have had to withstand months of this physical and mental torture.Please do not allow this to be a life long torture. My daughter is unable to work as she needs to care everyday and night,as grandad I have had to financially support my daughters family ,as my daughter is unable to work,which has placed very serious financial stress on us all, please help my family to cope with Pfic"	

Name	[redacted]
Role	Public

Other role	
Organisation	
Location	
Conflict	
Notes	
Comments on the ACD:	
"[redacted], a current PFIC patient, urgently requires this treatment to give her the life she so desperate deserves. As a parent myself, I can not comprehend just how mentally and physically challenging this must be for her parents. The persistent stress and anxiety waiting on results and endless hospital admissions with no solutions. But despite this adversity, they have shown incredible strength in supporting [redacted] through this difficult time. This drug has been life changing, provided some relief and hope of a better future for them all. [redacted] is a baby that will one day have goals and aspirations that she will look to achieve. She deserves the opportunity, like any other child, to realise her full potential. This drug is pivotal to that and so please do not deny her that equal opportunity."	

Name	[redacted]
Role	Public
Other role	
Organisation	
Location	
Conflict	
Notes	
Comments on the ACD:	
PFIC medication needs to continue to be available on the NHS	

Name	[redacted]
Role	Public
Other role	
Organisation	
Location	
Conflict	
Notes	
Comments on the ACD:	
"Its heartbreaking to have watched [redacted] and her parents struggle with this disease the past 10months I have known them . I first met [redacted] at swimming and she was a tiny little dot. After talking to [redacted] about [redacted] illness I was saddened and greatful for the health of my own baby just a few months older than [redacted]. We soon noticed [redacted] was always waiting on doctors calls or hospital appointments and stressed worrying about [redacted]. [redacted] was very unsettled during swimming classes and it was hard to watch a tiny baby clearly in discomfort and unhappy but as a mum [redacted] was just trying to do a normal mum and baby activity but it was clearly difficult. I learnt when getting to know [redacted] better that a lot of things were difficult for her due to her illness. Her allergies and struggles with food which are clearly from the stress of the disease on [redacted] body. I can't imagine how this must be for [redacted] family. Sometimes it's hard being around [redacted] with my own son as he is so blessed to be healthy and I feel so bad watching [redacted] struggle with normal life.	

Its heartbreaking that the medication that [redacted] needs and would be best for her isnt available on the NHS. Your liver is such an important organ and something completely out of a parents control to be able to keep and eye on and monitor. I hope [redacted] gets the medication she and her family deserve."

Name	[redacted]
Role	NHS Professional
Other role	Consultant in Paediatric Hepatogy, Chair of BSPGHAN Liver Steering Group
Organisation	
Location	
Conflict	
Notes	
Comments on the ACD:	
"The document is detailed and the review of the evidence is very comprehensive. The overall clinical need for a medical treatment for all types of PFIC (1-6 etc) remains tremendous as these are debilitating conditions. The long term outcome of patients undergone SBD and LT is not that well reported albeit NAPPED consortium put together the largest database of PFIC patients. The paediatric hepatology community across the UK and abroad have been making great efforts to treat these children in a more tan just a symptomatic way. There has also been reluctance from specific patient groups of PFIC1 patients to engage with LT due to poor outcome. These patients have no other alternative treatment and are subjected to a life of pruritus, sleep deprivation, poor QoL, missing out on education and subsequently on getting a job and reaching their full potential. Another point to consider in terms of effectiveness is that patients were recruited in the odevixibat study at various points in the childhood and older children had already suffered extensive damage to their liver and subsequently their life was affected to such an extend which are not be reflected in the measured outcomes. It would be of great interest to consider the long term beneficial effect the drug would have to a child starting treatment at 6 months of age (when crucial neurodevelopment and growth is taking place) and and their family compared to the older children who may have already been debilitated by the disease for years and they can only see the short term effects. The costs of 20 yrs worth of LT care and immunosuppression including all possible complications such as rejection, biliary and vascular problems will need to be compared with the same time period on odevixibat. Factors such as drug patent and competition will need to be calculated into the cost/benefit comparison. Patients with PFIC 4,5,6 etc are so few in numbers and they are at risk of not having any other treatment medicinal agents developed for them leaving odevixibat their only non-surgical option.For those patients we don't even have the long term LT outcome to compare with."	

Name	[redacted]
Role	Public
Other role	
Organisation	
Location	
Conflict	
Notes	
Comments on the ACD:	
"I am commenting on this consultation from the point of view of a family friend of a child who has just been diagnosed with PIC. I have had the wonderful [redacted] as a	

friend for a decade, but supporting her over the last 12 months has been heartbreaking. [redacted] gave birth to [redacted] last October and from the very beginning it was clear that [redacted] was ""struggling to thrive"". She was unable to digest [redacted] breastmilk, had chronic diarrhoea and sickness and was unable to sleep for any great length of time.

Thankfully [redacted] is the most stubborn person I know, she refused to give up until she had an answer to the problems which [redacted] faced. Without her persistence and instance that a diagnosis be found, [redacted] would still be in no mans land. Despite the diagnosis of PIC being devastating for the family and friends, the one glimmer of hope was the Odevixibat drug, which doctors said would slow the process of cirrhosis and reduce pruritus.

This drug would be life changing for [redacted] and for her family. The severe itching will impact [redacted] sleep, her capability to learn & attend normal school. Without the drug she will be in a constant state of pain, itching from the inside out, whilst her liver slowly degenerates and fails. [redacted] and [redacted] fought hard to get the rare diagnosis early for [redacted], and this should mean that any treatment can be applied early thus limiting the damage caused to the liver.

Without the approval of this drug, [redacted] will most likely need a liver transplant before the age of 10. The committee needs to assess the cost of the operation, the impact on [redacted] quality of life whilst waiting for a donor, whilst on immunosuppressant drugs and the recovery time from the operation. The cost to the NHS for the operation for a liver transpant and the life long care which she will need, should also be taken into account.

It was found by the committee that there was no guarantee that the drug would work for all types of PIC, but with such a rare disorder I question the ethics of not trying. It is estimated that less than 0.002% of the population have progressive familial intrahepatic cholestasis, a tiny number of people in the UK. Very little is known about the disease and yet it is debilitating and life limiting. It would be heartbreaking to watch [redacted] grow up without trying Odevixibat, knowing that it may enable her to live a relatively normal, itch free life and limit the damage to her already fragile liver.

If the scientific community in the European union and the United States can see the potential benefit of this drug then why can the UK not? If it truly is an issue of cost then the algorithm used needs to be reviewed. I cannot possibly see how any algorithm can not come down in favour of increasing a child's quality of life, reducing the need for a liver transplant and enabling her to sleep, learn and grow like a normal child.

Please reconsider the decision. Think of all the other [redacted] who's lives could be made brilliant by the approval of this drug."

Name	[redacted]
Role	Public
Other role	
Organisation	
Location	
Conflict	
Notes	
Comments on the ACD:	

The availability of medicine that can help the lives of those suffering from this rare disease shouldn't even need discussing. The medication is there and should be available. Imagine if it was your child who needed this and it was not available in the UK. What society would say no and refuse treatment.

Name	[redacted]
Role	Public
Other role	
Organisation	
Location	
Conflict	
Notes	
Comments on the ACD:	
"I have been extremely disappointed by the outcome of the draft decision not to recommend odevixibat for the treatment of PFIC to those suffering over the age of 6 months. My close friends' daughter heartbreakingly suffers from this condition – which will likely mean she will need a major operation of a transplant before she's 10 years old. [redacted] has just turned one and this medication will dramatically change her quality of life. A life which up to now has been a life of discomfort; with digestive issues and weight loss that has led to multiple hospitalisations and constant medical testing. To add to this further because of this distress and pain [redacted] has had extreme sleep issues which has not only impacted her but her family who are experiencing overwhelming levels of stress due to lack of sleep and concern for their first child. [redacted] disease impacts her parent's life not only emotionally but in a practical manner – how will her parents be able to attend hospital visits at the same rate that they have been and still keep their jobs? The toll of this stress has been monumental. Not only am I deeply concerned going forward about [redacted] physical health – but what about her mental well-being? as she approaches nursery and school age, how is she meant to have any sense of a normal life if she can't sleep? If she continues to live in a life of discomfort? [redacted] should be allowed the chance to thrive and succeed – and her family allowed a sense of relief - and this drug will have an enormous impact on this and therefore should not be limited to children under 6 months. Please reconsider your draft decision as the impact this will have for families and patients will be game changing. "	

Name	[redacted]
Role	Private Sector Professional
Other role	
Organisation	
Location	
Conflict	Previously supported this family when in an NHS role, continued support when moved into independent practice.
Notes	
Comments on the ACD:	
"I am a health professional that has been supporting a family who have a child diagnosed with progressive familial intrahepatic cholestasis. I am writing to ask the committee to fully consider the impact medication for this disorder could have on the whole family. The impact of a child possibly needing a liver transplant has a huge emotional burden for all the family. This kind of operation would hugely impact the child's	

education, emotional well being and mental health. The financial cost of the treatment, hospital care, medication following a transplant would be hugely costly financially but doesn't account for all other harmful impacts this would have on the outcomes for the child. Quality of life being improved will benefit not only the health service but the family and the child's potential throughout their life.
Please continue to consider the holistic view of the benefits to a child, family and the health service that a preventative therapy may have.
Many thanks
[redacted] "

Name	[redacted]
Role	Public
Other role	
Organisation	
Location	
Conflict	
Notes	
Comments on the ACD:	
This could be life changing. Please consider very carefully why this little girl should not get the medication Odevixibat which could change her life and future outcomes if she requires a liver transplant in the future.	

Name	[redacted]
Role	Public
Other role	
Organisation	
Location	
Conflict	
Notes	
Comments on the ACD:	
This medication should absolutely be made available on the NHS. There does not currently appear to be an effective alternative and moreover, early trial results for Odevixibat have demonstrated extremely positive outcomes. Whilst financial cost is clearly a factor for consideration, it should not and must not be rated more highly than the immeasurable value added to the quality of life for sufferers.	

Name	[redacted]
Role	Public
Other role	
Organisation	
Location	
Conflict	
Notes	
Comments on the ACD:	
"My niece, [redacted] aged 1 year, has been in pain, distress, underweight, and generally failing to thrive since her birth. She was eventually diagnosed with PCIF3. When I was told by her devastated parents that this was a life limiting illness and that her only hope for any sort of normal childhood was the break-through drug Odevixibat - which has already been approved for funding in Europe – is to be denied to her basically on the grounds of cost/value for money I too was devastated.	

How can you put a statistic on the life and or quality of life of a child? More to the point, how can you condemn any child to constant pain, discomfort, stress and probably the need for a liver transplant plus the ensuing draconian drug rejection regimen (assuming a suitable liver is available) by the time she is 10? This will be what she and her family must look forward too unless NICE approve Odevixibat for distribution on the NHS.
Her parents and family are all suffering with her, she is a treasured child, and we all want her to be given the best chances for a normal, happy childhood.
This is in the hands of NICE, when it should only be in the hands of God!

[redacted]

Name	[redacted]
Role	Public
Other role	
Organisation	
Location	
Conflict	
Notes	
Comments on the ACD:	

I'm commenting on behalf of [redacted], a patient that is currently battling PFIC. [redacted] has just turned one, and is fighting a hard battle against PFIC. In her first year of life she's been hospitalized multiple times, and is likely to have to have a liver transplant by age 10. As a close friend of her parents, I've seen the trauma that's impacted [redacted] illness as a family - sleepless nights, worrying about their little girl.

Name	[redacted]
Role	Public
Other role	
Organisation	
Location	
Conflict	
Notes	
Comments on the ACD:	

"It's absolutely devastating to hear the initial decision that odevixibat will not be recommended for the treatment of PFIC. As a close family friend of a 1-year-old PFIC type 3 patient, I've seen first-hand the enormous impact that this disease has had on the entire family in what should have been a joyful and exciting first year of [redacted] life.

Ever since [redacted] was born, she has been in and out of hospital for invasive and upsetting tests – the stress and strain that this has put on the entire family is huge, but with the impact of coronavirus on top of this it's been exacerbated to the extent where we've genuinely been concerned for the wellbeing of her parents, [redacted] and [redacted], and unsure of how they'll cope. [redacted] has been breastfeeding [redacted] since birth and therefore has had to be the parent to attend the hospital with [redacted] every time she's been admitted. This understandably is a huge pressure on [redacted] as well as being incredibly heart-wrenching for [redacted] that he can't be with them both in hospital. The stress and devastation that their child is unwell has transpired in severe bouts of anxiety and depression for both parents.

It was incredibly worrying when time and time again the health visitor would visit only to be told [redacted] wasn't putting on weight and they were concerned for her

growth. Every contact from [redacted] brought more devastating news about [redacted] health and development and it was heart breaking to not be able to help. When [redacted] finally received the diagnosis, it was initially a huge relief. It answered so many questions and felt like a positive opportunity to get things back on track and for [redacted] to have the happy and healthy childhood she so deserves. However, it only took a small amount of research to learn that actually the diagnosis was not the end goal we'd all hoped for, as it revealed the many challenges and struggles [redacted] would continue to face throughout her life.

As well as this disease causing [redacted] discomfort, problems with sleep, severe weight loss, and multiple hospitalisations, [redacted] also has a plethora of different allergies she suffers from as a symptom of her digestive system struggling with the disease. Her diet is incredibly restricted as a result, and, because [redacted] has continued to breastfeed to provide [redacted] with antibodies to help her weakened immune system, it's also meant that [redacted] diet has been limited to extremely basic foods for a year as well. I've seen [redacted] lose a huge amount of weight as a result of this, combined with stress, and am often concerned to not see her able to eat anything because [redacted] allergies are so severe and sensitive.

This disease is aggressive and brutal and the thought of a young child struggling with the symptoms when they should be growing, learning and enjoying life is unspeakable. [redacted] has just started nursery and [redacted] has returned to work, but how long this will continue for is unknown as there's so much uncertainty about [redacted] health. Not only does this have financial implications for the family but it could also have huge implications to [redacted] development if she can't commit to being well enough for nursery and school later on. The symptoms that come with PFIC will make it incredibly difficult for her to be comfortable and strong enough to learn and will also have an impact on her confidence and ability to socialise and enjoy herself as she grows up. If this medication could potentially prevent [redacted] from eventually needing a liver transplant it would drastically improve quality of life for her and her family.

For there to be a medication that could completely transform [redacted] life out there, but for it to be deemed as not providing 'value for money', is as infuriating as it is heart breaking. We beg you to please reconsider this decision. The quality of life for a child cannot be measured in terms of finances. [redacted], and the other sufferers, deserve a happy and healthy life, and this medication is the key to that."

Name	[redacted]
Role	Public
Other role	
Organisation	
Location	
Conflict	
Notes	
Comments on the ACD:	
"The use of Odevixibat for young children which may reduce or nullify the requirement for surgeries and other negative responses to the disease is beyond question. On both a practical and humanitarian level the welfare of the children and their parents should be paramount."	

Name	[redacted]
Role	Patient
Other role	

Organisation	
Location	
Conflict	
Notes	
Comments on the ACD:	
Everyone affected by PFIC deserve the right to be given the medication Odevixibat. Our beautiful Niece [redacted] has had a really tough first 12 months of her life which has had a huge affect especially on [redacted] and also on her doting parents who have spent many sleepless nights worried sick about [redacted] and endless hospital trips . The worry for all of us has been unbearable and we hope you will reconsider your decision and make Odevixibat available to [redacted] as soon as possible so she can start to thrive on the medication she deserves .	

Name	[redacted]
Role	Public
Other role	
Organisation	
Location	
Conflict	
Notes	
Comments on the ACD:	
Please support this very needed medication, a dear friends baby is poorly and in need of this very needed medication Thankyou	

Name	[redacted]
Role	Public
Other role	
Organisation	
Location	
Conflict	
Notes	
Comments on the ACD:	
This drug has had such a huge positive e benefit on my niece [redacted] life. I have seen how it has allowed her to be so much more engaged with life and be much more of an active, happy little girl.	

Name	[redacted]
Role	Public
Other role	
Organisation	
Location	
Conflict	
Notes	
Comments on the ACD:	
[redacted] is my friend's little girl. She's just turned 1 on the 30 September and it's been such a bumpy road for her and her family. In particular it has been a stressful and worrying few months for her mum, [redacted] and her dad, [redacted]. [redacted] condition went undiagnosed for months and the impact this has had on her parents but mostly [redacted] is so sad. She has had to endure constant hospital visits, intrusive tests and suffering. The whole family have been under so much pressure and their main aim and priority has been to get [redacted] better. Other aspects of their lives have had to be put on hold and they have missed out on enjoying the first year of their baby's life. It's so upsetting to see the worry and the anxiety they	

are enduring. [redacted] condition has resulted in sleep issues, eating issues and impacted on her weight and growth. As their friends we are extremely worried about [redacted] future and theirs. They are beyond committed to getting their little girl better and they are desperate to do anything.

Name	[redacted]
Role	Public
Other role	
Organisation	
Location	
Conflict	
Notes	
Comments on the ACD:	
A medication that is so life-changing should be publicly funded. When it's possible to avoid needless suffering, all efforts to should be made to do so.	

Name	[redacted]
Role	Public
Other role	
Organisation	
Location	
Conflict	
Notes	
Comments on the ACD:	
Life changing medication such as this should be made available under the NHS. Making health care affordable and available to everyone is perhaps the most nobal endeavour human kind has made.	

Name	[redacted]
Role	Public
Other role	
Organisation	
Location	
Conflict	
Notes	
Comments on the ACD:	
"Dear NICE, Please reconsider your decision to recommend Odevixibat for the treatment of progressive familial intrahepatic cholestasis (PFIC). The mental and physical impact of PFIC has been traumatic for my Niece [redacted] and her parents in her first year, the whole family have been suffering from [redacted] sickness and discomfort from her digestive problems, lack of sleep, as she is unable to settle or sleep because of symptoms, this is causing constant disruption to their lives, earnings, including the ongoing medical testing, the many hospital visits and constant worry about [redacted]. [redacted] has also noticeably suffered with poor weight gain and weight loss due to the lack of vitamin absorption. Unless she is given the chance of odevixibat [redacted] future is unfortunately not going to be a positive outcome and her quality of life will continue to be extremely poor. If odevixibat is available to [redacted] she will be able to thrive and the future will mean she won't have to suffer daily discomfort, she won't need to have constant care and won't have to have constant visits to hospital or develop other problems	

that will occur from the lack of vitamin absorption and most importantly she will not need a liver transplant (which would definitely incur high costs, might not work and also include the need for further lifelong medication).
[redacted] and her mum and dad and others like them could benefit immensely from odevixibat, seeing their children thrive again and live normal lives and also be able to live without all of the worries of the physical and psychological pain of the child's future hanging over them everyday.
This valuable drug would massively improve her life as it has in the trials and others who are taking it.
The NHS need to be able to offer odevixibat to give their patients with PFIC a better quality of life and most importantly - hope for the future.
"

Name	[redacted]
Role	Public
Other role	
Organisation	
Location	
Conflict	
Notes	
Comments on the ACD:	

"I am commenting on this consultation as the close friend of someone who's young child suffers from PFIC. I have seen first hand the impact this disease has had on the patient and carers quality of life, physical, mental and emotional health and well-being. Their young child has had significant care needs since birth and has been hospitalised on multiple occasions in her first year. The strain and pressure on her doting parents has been unimaginable and has significantly impacted their own health and well-being including being unable to work and experiencing significant health issues of their own as a direct result of the exhaustion and stress (their child was unable to sleep more than an hour at a time during her first 8 months due to debilitating itching, digestive problems and discomfort despite existing medication). Odevixibat would not only improve their child's quality of life it will also have a significant impact on improving the quality of life of her carers too (I.e. reducing the number of hospitalisations, improved physical and mental health and well-being and enabling them to work and live).

As a close friend of carers of a child of PFIC, I have been incredibly concerned about her parents overall health and well-being and the impact that barriers to diagnosis and treatment for their child due to the rarity of the disease has, and continues to have, on them and their child. I was incredibly disappointed to hear of NICE's decision to put up another barrier that would prevent them from gaining an improved quality of life.

I hope NICE will reconsider the regrettable decision not to reimburse Odevixibat. No child, person or carer should be denied what is potentially life-changing (and life-saving given the likely need for liver transplantation at a young age) medication for all those affected. "

Name	[redacted]
Role	Public
Other role	
Organisation	
Location	
Conflict	

Notes	
Comments on the ACD:	
"Odevixibat is the best opportunity available to [redacted] to lead the best life she can. As a 12-month-old child, it has been heart-breaking to see her in such pain and discomfort due to digestive problems, severe allergies, and severe itching. This has severely impacted on her sleep, nutrient uptake, and growth and development. Managing PFIC symptoms throughout [redacted] life has been overwhelmingly stressful for her parents, [redacted] and [redacted], who are close friends of mine. Due to Covid restrictions, they have carried much of the burden alone and it has been very hard to observe. Sleep deprivation and numerous extended hospitalisations have taken their toll on the family, so I fully support a treatment which could greatly lessen the burden on them. As a part of their wider support network, it would be reassuring to know [redacted] health would not deteriorate further. Without Odevixibat [redacted] future health is hugely concerning, especially the likelihood of needing a high-risk transplant whilst she is a still a child. This will not only prevent her having a normal happy childhood but will severely impact on her ability to attend school and receive a proper education. [redacted], and any child diagnosed with PFIC, wholeheartedly deserve the opportunity to receive Odevixibat and pursue a happy and healthy life. No child should suffer as [redacted] has done where it can be prevented."	

Name	[redacted]
Role	Public
Other role	
Organisation	
Location	
Conflict	
Notes	
Comments on the ACD:	
"Firstly, thank you in advance for taking the time to read this comment. I am writing to urge you to approve the use of the PFIC drug treatment Odevixibat on the NHS. My close friend [redacted], gave birth to her daughter [redacted] last September (2020). Since birth [redacted] has struggled to gain weight, suffered from various allergies and was classed by doctors as 'failure to thrive'. After many hospitalisations, tests and various treatments, it was discovered that [redacted] has PFIC. Since then she has been on medication to help her liver which has made some improvements on her health. However it hasn't been as effective as hoped and she still goes through periods of being poorly. Her doctors believe placing her on Odevixibat will significantly improve her condition and allow her to lead a normal healthy life. Currently her chances of needing a liver transplant by the time she's 10 are very high and the percentage of her not surviving this are around 10-15% - which as you can imagine, is a horrendous thought. [redacted] health has had an enormous impact on both [redacted] and [redacted] lives. [redacted] has spent a large proportion of the pandemic caring for [redacted], without being able to have any support in person from her friends and family. She is a wonderful mother who has done everything she can to help [redacted]. Despite all of the difficulties [redacted] has faced, she is a happy, strong and gorgeous baby who deserves the chance to live her life without the looming probability of a liver transplant. Therefore I urge you to approve the availability of Odevixibat on the NHS and give [redacted] the best chance of a normal healthy life.	

"

Name	[redacted]
Role	Public
Other role	
Organisation	
Location	
Conflict	
Notes	
Comments on the ACD:	
My son and daughter-in-law's beautiful one year old niece suffers with PFIC . This has had a traumatic effect on all the family, living with this potentially life threatening illness that [redacted] has. This thought clouds the years ahead of the love and enjoyment that most parents take for granted. If the medication was made available through the NHS to children with this condition it would make such an amazing difference for this little girl and her parents .	

Name	[redacted]
Role	Public
Other role	
Organisation	
Location	
Conflict	
Notes	
Comments on the ACD:	
" [redacted] is aged 1 year, and she has been distressed , underweight, and generally failing to thrive since her birth. She was eventually diagnosed with PCIF3. I understand that this is a life limiting illness and that her only hope for any sort of normal childhood is the break-through drug Odevixibat - which has already been approved for funding in Europe. NICE's decision not to make this drug available on the NHS, will deny her the chance of a healthy childhood basically on the grounds of cost/value for money. Obviously, all drugs have to be evaluated for cost effectiveness, but this is a child in her first year and Odevixibat appears to be the only effective drug at present. It will give her a normal quality of life, as opposed to constant pain, discomfort, stress and probably the need for a liver transplant plus the ensuing draconian drug rejection regimen (assuming a suitable liver is available) by the time she is 10? This will be what she and her family must look forward too unless NICE approve Odevixibat for distribution on the NHS. I would urge NICE to seriously consider making this drug available [redacted]	

Name	[redacted]
Role	Public
Other role	
Organisation	
Location	
Conflict	
Notes	
Comments on the ACD:	
"For the last year I've watched in sadness and helplessness [redacted] has been constantly ill. I've found it incredibly difficult to watch [redacted] and [redacted] turn themselves inside out trying to make life better for [redacted] and in turn found it	

heartbreaking to watch a new life have to struggle so much and fight so hard just to survive. [redacted], in an effort to ease [redacted] dietary struggles whilst breastfeeding and through sheer stress, has lost so much weight, is exhausted and so on edge that I worry for her health. [redacted] has been through his own traumatic health problems this year, owing in a large part to stress. This is not to mention the financial worries this is already causing for their family, that will only increase as [redacted] condition worsens.

[redacted] is smart, funny, sweet and cheeky and has a whole army of people who want to see her thrive and grow, but whilst we can offer love and time to support the family, we all remain helpless in the absence of the medicine needed to help improve and sustain her quality and longevity of life. [redacted] and [redacted] keep doing so well to build up her weight and strength, then a small setback knocks her back down again. It has been a constant worry to her family and their support network having [redacted] in and out of hospital constantly, with the mental and physical trauma for her having to keep undergoing tests including having to go nil-by-mouth when she is already starving and massively underweight. At the moment, [redacted] is too little to understand and retain too much of the memory, but this will not be the case for much longer.

Yet in the face of her illness, [redacted] continues to develop an independent, strong-willed and intelligent personality. I worry that this will be greatly stunted and impacted by her illness and the subsequent symptoms, disturbing her ability to attend school, socialise with other children and even sleep well and concentrate. Having read success stories of other babies being able to rely on this treatment and the harrowing stories of those whose children have had to struggle without it, I urge you with every fibre of my being to reconsider your decision to fund this drug on the NHS. Please, please give [redacted] and other children like her the chance to thrive and live happier, healthier lives."

Name	[redacted]
Role	NHS Professional
Other role	Consultant
Organisation	
Location	
Conflict	"I am currently subinvestigation in the PEDFIC2 trial. I have been paid by Alberio to take part in the virtual advisory board meeting on Odevixibat"
Notes	

Comments on the ACD:

The document informs that the effectiveness of odevixibat is uncertain. However, there is clear evidence from the trials that odevixibat reduces serum bile acids and improves pruritus in FIC1 deficiency and BSEP deficiency patients.
Liver cancer is not a complication of liver transplant.
Long term native liver survival rates are clearly documented in the NAPPED data for BSEP deficiency.
PFIC is a rare disease and hence, conducting large scale trials is not possible. In addition, it will take a very long time to conduct a trial with large numbers of PFIC patients.
In the clinical setting, response will be determined by patients report of improvement in itch and dose escalation will be directed by patient and family's feedback. The primary indication for starting odevixibat in clinical practice will be for itching and if there is improvement of itch, then the medication will be

continued. The difference in response in different doses may be influenced by other factors like seasonal variation (eg, winters when heating is on).

Name	[redacted]
Role	NHS Professional
Other role	
Organisation	
Location	
Conflict	
Notes	
Comments on the ACD:	
Cost effectiveness should be taken into account, but also the impact on the child of transplant, recovery and long term medication by antirejection drugs. There is also a limited number of transplant organs and so if medication can avoid transplant this can only be positive.	

Name	[redacted]
Role	NHS Professional
Other role	
Organisation	
Location	
Conflict	
Notes	
Comments on the ACD:	
As a paediatric nurse and a great respect for NICE guidelines in my work, I am hoping that the drug odevixibat for PFIC that NICE have decided not to recommend for children over 6 months will be reconsidered instead of leaving these children to have life saving therapy for end stage liver failure. My great niece, who is just one has struggled already from birth. She has failed to thrive, not slept and caused post natal depression in her mum and her dad has had a heart attack at 31 which we are all convinced is due to the stress of the effects of the illness and of what the future holds for their beautiful daughter and themselves. The effects on their very new family has already been devastating. No sleep for anyone, mum can't go back to work as she can't leave her daughter with anyone due to appointments and tests and pressure on Dad to earn more to support and the worry that this has caused. Imagine not sleeping for months. This will continue with the devastating symptom of pruritus which will in turn cause a diminished quality of life for the whole family amd affect her education and socialisation. Its a life changing drug that is available but not funded which as this is a rare condition is so sad. I understand the need to carefully decide on the cost v's effectiveness of any new drug but I wanted to share the psychological affects on not only my great niece but also her immediate family and extended too. The stress of knowing that by the age of 10 their child would need a transplant-knowing the waiting times and anxiety that this will bring to everyone involved on a daily basis. Not only this but she will have to take immunosuppressant drugs for the rest of her life if she has a transplant which leaves her open to infection, many hospital stays and these are too very expensive.	

With odevixbat her quality of life would be so much better and she wouldn't miss out on school etc - if she's so ill that she needs a transplant then she would suffer and miss out on so much.

"The suffering and quality of life for children with PFIC is terrible. The approval of Bylvay gives parents tremendous hope as the first drug treatment now available," said Alison Taylor, Chief Executive of Children's Liver Disease Foundation (CLDF). "The decisions we have to make as parents are hard enough, but for PFIC parents they might have to consider surgery and liver transplantation for children, while managing an immense disease burden that affects the entire family."

With no serious side effects and excellent results on reductions in serum bile acid, pruritus and growth- these children need this.
They didn't choose to have it and the families certainly wouldn't of done.
Surely it's morally wrong to fund drugs for illnesses related to harm one can cause to themselves and not a drug like this. These children deserve to have the best quality of life that is possible and this drug will do this.
Thank you in advance

Dear NICE Evaluation Committee,

Thank you for allowing our organization, the PFIC Network, an opportunity to comment on the initial decision for the guidance on using odevixibat in the context of national commissioning by NHS England. As the only patient led organization that represents PFIC patients and families, including those in the UK, we are grateful for the opportunity to comment during the public consultation period.

While your committee has made an initial decision not to recommend reimbursement for odevixibat in the UK, England and Wales, we understand the importance of this opportunity, and want to share with you another side of PFIC and the promise that odevixibat brings to PFIC patients and their families.

As you know, many PFIC patients are diagnosed in the early parts of their lives. Some at birth, others in their toddler years, and few in adolescence. Because of the age of diagnosis and onset of symptoms is so young, PFIC becomes a disease that affects not only the individual, but also every member in the family. I can tell you firsthand, as a mother of two children with PFIC, this disease will wind its way into every part of a family's life. The relentless itch that we have all come to know very well in PFIC makes living a "normal" life nearly impossible. Sleep disturbances, treating damaged or broken skin, and the emotional toll of trying to comfort a child who wants nothing more than to stop itching are just a few ways PFIC affects us.

The Itch

Dealing with itch is more than just an itch—families lose jobs, children can't attend school, parents feel helpless, siblings feel neglected—all because of itch. PFIC itch becomes so intrusive that families are left looking for anything to help their child feel relief.

These are excerpts from testimonials of families who were asked to talk about their experiences with itching.

> *The pruritus was increasing and no balms for atopic skin helped, and no allergy medications and sedatives. I kept her nails short. I think that only someone with a similar disease will understand us. The itching caused her to sleep for 15 minutes and wake up crying and scratching constantly. I was taking her hands away because she was scratched to blood, but she was still doing the same. It was like a fight. At night, when it was dark, I knew she was scratching because I could smell her blood. Nobody wanted to care for her during the day because they were afraid of her scratching attacks. Besides, she just wanted to come over to me. This tiredness on our part was so great that I thought that I would commit suicide because in our house there was only crying and nerves between us in the household. Fatigue, lack of sleep, stress.*
>
> *The nights were the worst. I only remember a terrible cry, often screaming, scratching herself to the blood, torn ears, and a nose with scars so deep. Due to the lack of sleep, she was always angry and irritable. I couldn't watch how much my beloved child was suffering ... This itch cannot be compared to anything else.*
>
> [redacted] *kept scratching herself to the point of blood. She woke up crying, she could not sleep because the itching of the skin was so increasing that she could not stand the pain. More than once I heard from people, family friends, why is she so scratched?*
>
> *Life with* [redacted] *itching was extremely exhausting for our whole family, there was no way to help him, nothing brought relief. We put gloves on him, we held hands so that he wouldn't scratch himself, which made him cry even more. He couldn't sleep because after a few hours he was awakened by itching. It is so strong that even in publications you can read that in extreme cases it can cause suicide*
>
> *One of the most challenging things we have had to endure is watching him harm himself while scratching to try and relieve himself from the intense sensation of pruritis*

Here are further testimonial on how pruritus can impact the whole family:

> *My daughter has PFIC 2, we watched her as a newborn and for the first year of her life suffer a non-stop, torturous, painful, endless horrendous itch that covered her entire body. She cried non-stop, slept for only 15 minutes at a time, she was never still and tried to scratch any way she could, her skin was full of scabs. she would only get three to four hours of broken of sleep every 24 hours. My then, two-year-old son suffered terribly with parents that barely slept and a new sibling that was writhing in pain. The itch was so bad that my intense fear of transplant was overtaken by the need to get rid of this itch, it was destroying her life and that of my families. I felt sick to my stomach because the research and statistics on liver transplant are not so good, going through a*

transplant is a horrific experience in itself and even if we had a transplant, she had to endure months or perhaps years of this unbearable itch while she waited for an appropriate liver to become available.

My daughter has PFIC 2 and is awake all through the night, crying in pain due to the itching. Her 4 year old brother has nightmares due to her constant cries and her pain. He does not sleep well and acts out at school. His classmates tease him because his sister has scabs all over her body. He got in a fight at school as he was defending her. One day, he told me that he wanted to go live with his grandfather, so that he does not need to hear [redacted]'s cries.

This is what PFIC itch is like.

It is more than "just an itch"--it is a condition for which there is no relief, leaving patients and families desparate for help.

Surgeries & Transplant

Families even **chose** transplant—risking their child's life—to try for a chance to help their child stop itching.

Can you imagine? Choosing an expensive, devastating, risky, intrusive, life-changing surgery in order to help your child not to itch.

[redacted], a mother of a child with PFIC, shares her family's experience with a decision of surgical interventions:

*The current treatment is not a treatment at all. Kids end up taking various medications that may or may not reduce their symptoms, and often come with a lot of other detrimental side effects. When these don't work or when they stop working, the next and only other option is to undergo invasive surgical interventions. My child has had 5 surgeries to manage their disease; two of them were due to life threatening complications of previous surgeries. I find it reprehensible that access to a medicine that could treat pruritus and stop disease progression would be withheld in favor of risky surgical intervention…. **The cost of "managing" PFIC with the current options is extraordinary**. For example, our family has spent over 6 months of the last 12 months in the hospital due to transplant and transplant related complications. Not only has that had significant impacts on the healthcare system, but it has also been detrimental to our child's quality of life and development. For our family, it has meant loss of jobs, reliance on social/governmental support programs, etc.*

[redacted], mum of 10 year old [redacted], shares her family's experience with a Partial External Biliary Diversion:

[redacted] is now 10 years old and has been working with a stoma in the small intestine for over 9 years. It is great discomfort and shameful for him in front of his peers but at the moment the only way to live…. He cannot fully function like other children. We tremble all the time so that nothing happens that would damage his stoma, we have no guarantee that the results will not worsen overnight. Having an ileostomy is also associated with the risk of dehydration, as electrolytes "escape" with bile, which has already caused [redacted] to be hospitalized several times. Any pharmacological method that would involve closing the stoma would be a huge step for us, and above all for [redacted], in improving the quality of life in every aspect (social, mental).

These are the options we are left with.

But it doesn't have to stay that way. Odevixibat is the only available treatment that has proven to stop the itch. Odevixibat is the first time PFIC patients and families have had a glimpse of hope.

Safe, life-changing, non-invasive, non-surgical hope.

Hope for a Better Quality of Life

Below are four testimonials from families who explain the impact that odevixibat has had on improving quality of life.

Our 14 year old son, [redacted], has been taking Odevixibat as part of an extended trial since May 2019. Since then, we have seen a dramatic reduction in the itching that comes with his PFIC2 diagnosis. He can now sleep through the night for almost the first time in his life. Prior to starting the medication, he was so massively sleep deprived and itchy that we considered taking him out of school. We thought we were heading towards an inevitable transplant due to intolerable pruritus. [redacted] could not concentrate on his schoolwork and often needed to have a nap in the middle of the day. His itching particularly affected his legs and feet and these were always scabbed,

scarred and bloody. Every night, he would get blood on his sheets. The whole family suffered from sleep deprivation along with [redacted]. He was not able to sleep in a room on his own. He can do this now. The scars on his legs have started to fade. The whole family is more rested. [redacted] can now concentrate more effectively on his schoolwork and enjoy his leisure time without the constant need to itch. He has a more positive outlook and so do we! We couldn't imagine doing without the medication now. No other treatment is available that effectively addresses [redacted]'s pruritus. Without it, his educational and mental health outlook would be very bleak. The essential visits to hospital and to mental health professionals were much more frequent before starting on Odevixibat. ***In short, it has saved our son and our family from a most dismal future and greatly reduces the prospect of overutilizing our national health resources****.*

Our teenage son has been on Odevixibat for several years now to reduce itchiness brought on by his PFIC TYPE 2 condition. The medication has been life changing for him. He used not to be able to sleep due to scratching all night. This caused both tiredness and inability to concentrate at school (along with his itchiness) taking many years of education off him. He was tracking 3-5 years behind his peers. Since being put on the medication, he is still itchy, but to nowhere near the extent previously. He is catching up, and can concentrate during school. It seems to have also arrested the progressive deterioration of his liver. We are resigned to having daily medication into the distant future. However, ***we would much rather have medication supporting his own liver, than other medication stopping his body rejecting a foreign one****.*

My daughter [redacted] is 2.5 years old. She was diagnosed with PFIC type 2 when she was 3 months old. She had jaundice, enlarged liver and spleen, and vitamin deficiencies. She received medications, including Ursofalk and vitamins, which stabilized her condition at the time. However, one of the worst symptoms was yet to come. The pruritus started before the age of 1. Modest at first, she scratched her face, ears, and legs. It grew stronger with time. The nights have become very hard. She fell asleep for a while and woke up after 15 minutes screaming. We couldn't calm her down. Soon the itching began to bother her during the day as well. It often meant irritability, no desire to play, and looking for constant attention. It was hard to look at her suffering. After a few months, she was able to join the early access program organised by Albireo and received Odevixibat. We noticed less itching after a few weeks. After about 1.5 months blood tests, and liver tests results were much better, and bile acid level dropped dramatically. About 2 months after using it, we almost forgot about the itching. The life of our doughter and ours slowly returned to normality thanks to Odevixibat. [redacted] can play with children, take advantage of all children's activities. She develops correctly. I cannot imagine a situation that the drug that is helping her is available on the market but we are unable to get it because of high cost. At this moment ***Odevixibat is the only non-surgical option to deal with itching and let our daughter live a normal live.*** *PFIC patients and their families need it." --[redacted] mom of 2,5 years old [redacted]*

Our story began when my daughter was 3 months old and we were vaccinated by the doctor. An experienced doctor urgently sent us to the liver and general tests because our daughter was yellow. The results of the tests were very bad - jaundice and elevated liver tests where Asp and Alt were above 600. We went straight to the hospital, of course, she had an extended tests - from metabolic diseases to cystic fibrosis. I believed in a miracle that everything was going to be fine in the end, but this miracle never happened. We found ourselves in a specialized medical facility. There we found empathic doctors. We heard the diagnosis - progressive familial intrahepatic cholestasis. We got Ursofalk and vitamins. There was also a bleeding disorder because the INR was abnormal. The worst was just ahead of us when the baby started scratching because of the high bile acids. The pruritus was increasing and no balms for atopic skin helped, and no allergy medications and sedatives. I kept her nails short. I think that only someone with a similar disease will understand us. The itching caused her to sleep for 15 minutes and wake up crying and scratching constantly. I was taking her hands away because she was scratched to blood, but she was still doing the same. It was like a fight. At night, when it was dark, I knew she was scratching because I could smell her blood. Nobody wanted to care for her during the day because they were afraid of her scratching attacks. Besides, she just wanted to come over to me. This tiredness on our part was so great that I thought that I would commit suicide because in our house there was only crying and nerves between us in the household. Fatigue, lack of sleep, stress. She fell asleep only in the morning when she was tired from crying. When she cried, I cried with her. During the day, she never slept. I couldn't go back to work, and we also have other children. Our life and hope returned when we were referred to the investigational drug program for pruritus. My daughter got a genetic test and it turned out to be PFIC type 2. And we were given hope for improvement. Since my daughter started taking the drug, our nightmare began to disappear. Of course, her results are fluctuating, but the itch from the highest, i.e. 4, decreased to 1 on the itch scale. I can go to work which is very important to me. It is not the child's fault that she inherited the damaged gene and it is not her fault that she so far not found medicine for this type of itching. Every child should get treatment for free, and what should we do is that it is not free, and this is a price that parents cannot afford, who would do anything to help their child.

Our everyday life is filled with the fear of our child whether her bile acids will increase and our greatest enemy – the itch, will return. Coming back to these memories, I have tears in my eyes. Because my daughter is loved and so cheerful and she enjoys life, she attends a nursery. How would I take it all from her now? --Mom of 2 years old [redacted]

With this submission, we earnestly request that your committee reconsider you decision for reimbursement. Odevixibat gives PFIC patients an opportunity to feel relief from this debilitating itch that increases their chance of survival (compared to a liver transplant, the only other proven intervention to remove itch). And if you have time, please take a look at the other testimonies we have included with this submission. These are real people sharing their story of how their lives have been impacted by itch and how odevixibat has improved quality of life for their loved one with PFIC.

Thank you again for taking the time to hear our voice. We are rare, yet we are mighty.

Warm Regards,

The PFIC Network

NICE Submission-Patient Testimonials

"[redacted]'s is almost 2 years old, with PFIC type 2. The first year of life was very difficult for all of us because we did not know what we were dealing with and what this disease brought with it. The nights were the worst. I only remember a terrible cry, often screaming, scratching herself to the blood, torn ears, and a nose with scars so deep. Due to the lack of sleep, she was always angry and irritable. I couldn't watch how much my beloved child was suffering ... This itch cannot be compared to anything else. My daughter has had a stoma for a year (she was too young to join the experimental drug program), the itching has not completely disappeared, we still often have bad nights and days. Additionally, she has a pouch which also makes life difficult now, and when will she be older? I sincerely hope that you will hear us, because the heart hurts so much that we are so close to the medicine that inhibits this terrible itch, to saving our child and improving the quality of her life - and at the same time so far..."—[redacted], mom of [redacted]

"Hello, I will describe to you our history of intrahepatic cholestasis and the experience of itching that accompanied it. My daughter [redacted] fell ill in 2014. The first symptoms of the disease were intense scratching all over the body throughout the day and also after waking up at night. Additionally, there were spots of red color all over the body. All of [redacted]'s skin was covered with very itchy spots. The first presumptive diagnosis was protein diathesis, the next diagnosis was sensitization-allergy, the next diagnosis was scabies, all were wrong. [redacted] kept scratching herself to the point of blood. She woke up crying, she could not sleep because the itching of the skin was so increasing that she could not stand the pain. More than once I heard from people, family friends, why is she so scratched? I remember today when, after conducting a series of tests, she was diagnosed with the disease of intrahepatic cholestasis. Doctors explained to us what this disease is, what awaits us, I was terrified [redacted] switched to treatment with an experimental antipruritic drug, and it was only this that brought her relief. We have the worst memories of the preschool period, where [redacted] was rejected by her peers, no one wanted to play with her because of that itching. I explained that it is impossible to get infected with it, but it did not help. [redacted] did not want to go to school, she was crying a lot and her words remained in my ears: "mom, why is that, why don't the children want to play with me, stay with me?" I didn't know what to tell her ... having access to a cure for itching gives us hope for a normal life for her ..."--[redacted], mom of 7 years old [redacted]

"[redacted] was born prematurely (35 weeks in pregnancy) in April 2011. In the first weeks of his life, everything seemed to be fine except that he was gaining very little weight. Around 3 months of age, he began to sleep very restlessly, woke up, cried, and rubbed his face with his hands to such an extent that wounds began to form. We did not know then what was the cause. In August he was hospitalized with high bilirubin, it turned out that he had intrahepatic cholestasis, and bile acids were several dozen times above normal, other liver results were also very bad. After broadening the diagnostics, after a few months, he was diagnosed - PFIC-1. Life with [redacted] itching was extremely exhausting for our whole family, there was no way to help him, nothing brought relief. We put gloves on him, we held hands so that he wouldn't scratch himself, which made him cry even more. He couldn't sleep because after a few hours he was awakened by itching. It is so strong that even in publications you can read that in extreme cases it can cause suicide. This situation changed after the external bile drainage was performed. The test results improved and the itching decreased. [redacted] is now 10 years old and has been working with a stoma in the small intestine for over 9 years. It is great discomfort and shameful for him in front of his peers but at the moment the only way to live…. He cannot fully function like other children. We tremble all the time so that nothing happens that would damage his stoma, we have no guarantee that the results will not worsen overnight. Having an ileostomy is also associated with the risk of dehydration, as electrolytes "escape" with bile, which has already caused [redacted] to be hospitalized several times. Any pharmacological method that would involve closing the stoma would be a huge step for us, and above all for [redacted], in improving the quality of life in every aspect (social, mental). Soon he will be a teenager and then the situation will probably affect him even more. I know that many adolescents are unable to function with a stoma and it has to be closed with a risk of losing health and possibly life in the long term as liver cirrhosis will develop over time."--[redacted], mum of 10 years old [redacted]

"PFIC is a life altering, painful, traumatic disease that has left us feeling hopeless and desperate for treatment. We have a 4 yr old son who has been diagnosed with PFIC 2. The pruritis that he has experienced has effected his sleeping, his eating, his mental health and his quality of life. The pruritis is so intense that he is physically unable to sleep and physically unable to eat the majority of the time. This disease has robbed him and continues to rob him of a joyous childhood. One of the most challenging things we have had to endure is watching him self harm while scratching to try and relieve himself from the intense sensation of pruritis. This disease has not only effected our boy but it has rippled into effecting our whole family. The symptoms of PFIC effect how he plays with his siblings, how we as a family use our time and how we use our finances. We believe there is a desperate and urgent need for disease modifying treatments. Current medical options offer little to no symptom relief. New treatments would significantly increase the quality of life for those affected by PFIC. New treatment options would allow us not to have to put our child's life at risk by going through a liver transplant. If access to new treatments is denied it would leave us hopeless and devastated."[redacted], parents to 5 year old [redacted]

“PFIC is an absolutely horrible disease which has caused great pain and discomfort for our 4 year old grandson and his whole family. He was diagnosed with PFIC 2 as a young baby and not only do his parents have to worry about the damage being done to his liver and the fact that at any time it could fail and cause him to need a liver transplant but his quality of life has been incredibly impacted. He has lived with a constant uncontrollable, deep, all over 24/7 itch that is absolutely impossible to relieve. (Severe Pruritis) He scratches so hard that he bleeds, gouges, self harms and rips off his toenails just trying to get some relief but nothing works. He’s not able to sleep and is constantly tired which has also negatively affected his mental health. Many many times he is also not able to eat as he’s just too miserable from being so itchy which of course causes other problems such as weight loss. It is heartbreaking for his parents (and us grandparents) to watch and try to comfort him yet there is nothing any of us can do to help and it leaves us feeling hopeless. My daughter and son-inlaw are exhausted as well because they are up all the time at night trying to comfort him so he can get a little sleep. His siblings are affected too as their sleep is disrupted and they are not able to play with him many times as he is crying in pain and scratching instead of being able to play as a typical 4 year old should be. He has been on many different medications which have not worked for him in any way. New treatments for this disease would allow our grandson and other children with PFIC to enjoy life again having relief from the intense itch and pain from self-harm. New treatments could also possibly reduce the need for these kids to have a liver transplant which is a life threatening surgery that no child should have to go through. If access to new treatment options for this disease are denied our grandson and the other children with PFIC will continue to suffer 24 hours a day and families will be left feeling overwhelmed and hopeless. [redacted] and [redacted], grandparents

“My daughter has PFIC 2, we watched her as a newborn and for the first year of her life suffer a non-stop, torturous, painful, endless horrendous itch that covered her entire body. Nine years ago when she was born our only hope was a liver transplant and possibly diversion surgery. However, the team were not keen to transplant until her tiny body gained more weight and she was at least 12 months old, only then could she even be listed for transplant. I couldn’t believe there were no medications, no treatments whatsoever that could alleviate my baby’s pain. She cried non-stop, slept for only 15 minutes at a time, she was never still and tried to scratch any way she could, her skin was full of scabs. she would only get three to four hours of broken of sleep every 24 hours. My then, two-year-old son suffered terribly with parents that barely slept and a new sibling that was writhing in pain. The itch was so bad that my intense fear of transplant was overtaken by the need to get rid of this itch, it was destroying her life and that of my families. I felt sick to my stomach because the research and statistics on liver transplant are not so good, going through a transplant is a horrific experience in itself and even if we had a transplant, she had to endure months or perhaps years of this unbearable itch while she waited for an appropriate liver to become available.

In some cases, PFIC symptoms can come and go, episodic PFIC usually presents with onset at age 8 or older and it is very rare to be seen when a child presents as a newborn. However miraculously this was the case for my daughter, at around 12 months old symptoms began to ease. Episodic PFIC is not well understood but the one thing they do know and her doctor keeps reminding us of, is symptoms can return with a vengeance at any time. While my daughter has been mostly well for the past eight years, her mental health has suffered greatly from the trauma of the first year of life. This year after many years of struggling, despite being intelligent and sociable the toll of PTSD on her life has meant she has been unable to attend school and will now be home-schooled for the foreseeable future. She has seen two excellent paediatric psychiatrists both have made a clear diagnosis of PTSD due to the intractable itch and trauma of the first year of life. Missing milestones, failure to thrive, not sleeping and not being able to have ANY pain relief in the formative first 12 months of her life has had a devastating effect on my daughter’s mental health. For many PFIC children relief does not come until years later when they get a liver transplant or undergo diversion surgery. The toll is physical and mental and effects the entire family.

It is very clear if she had access to Odevixabt at diagnosis her life, my son’s life, my husband’s life and my life would very different. There are no other approved treatment options for PFIC that are safe and effective. The cost of transplant or diversion surgery on the health system and not to mention on a small child’s body, is a cost that all governments and families would want to avoid.

As a patient advocate for PFIC, I have supported many PFIC families. I have met families at their most desperate, and like my daughter and my family, they are not only dealing with a child in severe pain, but often they can barely function, are sleep deprived and very isolated. I have then gone on the witness the utter joy to watch many of these families who have been able to access Odevixibat on trial or via expanded access, go on to have their entire lives turned around. Their child whose bed sheets were covered in blood every night from scratching, who were unable to socialise or learn at school, are now able to sleep, play, learn and smile!!

There is no comparable treatment, this drug is saving lives, it is delaying or stopping the need for transplant, it is allowing children to not suffer ongoing mental health issues.

When a child is in this much pain the need for help is beyond urgent this is not an itch like eczema or any other skin issue, the itch comes from the inside and is unbearable. Odevixibat is a safe and effective treatment, it has had success in a number of subtypes of PFIC. I have mentored families with PFIC from a range of sub types all of whom have had success with Odevixibat." – [redacted]*, PFIC Mother and PFIC Advocate.*

Odevixibat for progressive familial intrahepatic cholestasis: A Highly Specialised Technology Appraisal. The ERG's response to the company's response to the ACD.

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Alastair Baker has been recruited to be the PI of a future study of odevixibat for cholestatic itch in Alagille syndrome (ASSERT), for which he will be financially reimbursed by Alberio. He has also received financial reimbursement from Mirum Pharmaceuticals to study cholestatic itch. No other authors or clinical advisors declared competing interests.

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Rider on responsibility for report

The views expressed in this report are those of the authors and not necessarily those of the NIHR HTA Programme. Any errors are the responsibility of the authors.

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Contributions of authors

Emma Hock summarised and critiqued the clinical effectiveness evidence submitted by the company. Praveen Thokala and Kate Ennis critiqued the health economic analysis submitted by the company. Geoff Holmes critiqued the statistical aspects of the submission. All authors were involved in drafting and commenting on the final report.

1 Background

NICE appraised odevixibat for treating progressive intrahepatic familial cholestasis (PFIC) at an evaluation committee on the 5th of August 2021. This resulted in an Evaluation Consultation Document (ECD) which did not recommend the use of odevixibat for treating PFIC in people aged 6 months and older.[1]

On the 11th October 2021, the Evidence Review Group (ERG) received documents, via NICE, from the company (Albireo) that provided a response to seven key issues raised in the ECD, and with a revised Patient Access Scheme (PAS; awaiting approval). The 9-page comment response and the 1-page Appendix are collectively referred to as the company's response to the ECD.

The original PAS took the form of a simple price discount of [redacted] on the list price for odevixibat, which was [redacted] per pack of 30 capsules containing 200 µg, 400 µg, 600 µg or 1,200 µg, respectively, resulting in PAS prices of [redacted], respectively.

The new proposed PAS is a [redacted]. The proposed PAS has not been formally agreed.

In this document, the ERG summarises the seven substantive comments raised by the company to key issues within the ECD and, where appropriate, provides a critique of these issues.

2 Comments raised by the company in its response to the ECD and ERG critique

For brevity, the position of the company has been summarised and then critiqued by the ERG within each section. The section headings follow the numbering of the company's comments in its response to the ECD. The first numbered comment by the company is an executive summary of their response. Therefore, we will only summarise and critique comments 2 to 8 in sections 2.1 to 2.7.

2.1 Availability of odevixibat for all PFIC subtypes

In the ECD response, the company acknowledges the statement in Section 4.1 of the ECD that the committee "*concluded that the clinical effectiveness of odevixibat by PFIC type was uncertain*" is true, and nevertheless suggests that "*odevixibat should be made available for the treatment of all PFIC subtypes in line with the licensed indication*".[1] The company justifies this position based on the rarity of PFIC4, PFIC5 and PFIC6, the views of the company's clinical advisors, the marketing authorisation, and accumulating data on the effects of odevixibat among patients with these subtypes.

2.1.1 Rarity of PFIC4, PFIC5 and PFIC6 and the views of the company's clinical advisors

PFIC4, PFIC5 and PFIC6 are the rarer subtypes of the condition, and the company presents evidence in the ECD response of a worldwide prevalence of 28, 9 and 36 cases of PFIC4, PFIC5 and PFIC6, respectively. Such low numbers of cases would present difficulties in conducting a clinical trial (particularly a randomised controlled trial) in these sub-populations. The company also argues that since the defining characteristics of all PFIC subtypes are elevated serum bile acid concentrations and intense pruritus regardless of the specific genetic mutation, odevixibat could reasonably be expected to improve these outcomes among all PFIC patients. The company consulted with clinicians in the field, who advised that "*cases of PFIC 4, 5 and 6 are extremely rare in UK clinical practice; however they would like the ability to prescribe the best treatment for these patients if or when they present*".

The ERG agrees that it would be impractical to wait for trial data for these PFIC subtypes, due to low incidence and prevalence rates, and also agrees that there is evidence for the mechanism of action of odevixibat in reducing elevated serum bile acid (sBA) and alleviating severe pruritus in a large proportion of patients with these biological and clinical indications. Clinical advice received by the ERG suggests that any chronic cholestatic disorder with pruritus but some degree of bile flow (i.e. not those patients with a complete absence of bile salt export pump (BSEP) protein) could be reasonably expected to respond to ileal bile acid transporter (IBAT) inhibitor treatment, in general terms, although one clinical advisor re-iterated that there is insufficient clinical data at present to say this with certainty.

2.1.2 Marketing authorisation

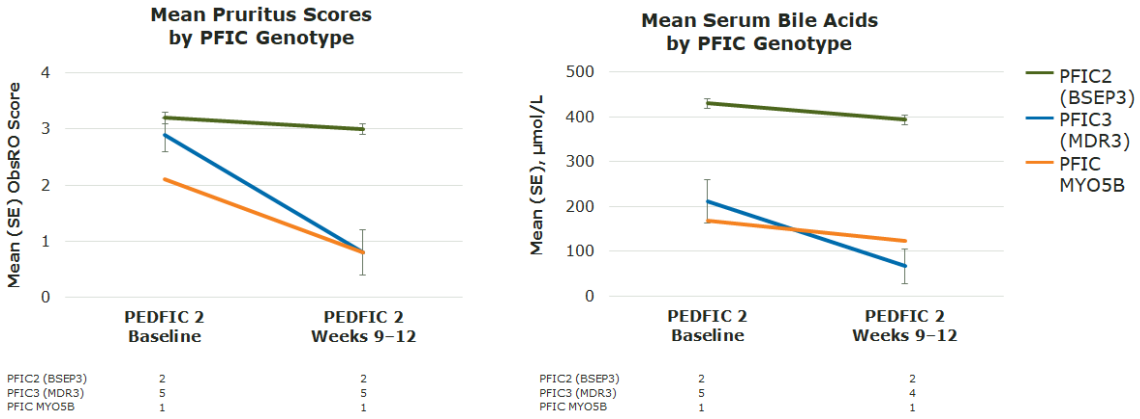
In the ECD response, the company states that marketing authorisation was granted to odevixibat by the European Commission on the 16th of July 2021 for the treatment of PFIC in patients aged ≥6 months. The company argues that the mechanism of action of odevixibat (inhibition of the IBAT in the terminal ileum) operates independently from the genetic markers that define the PFIC subtypes. The ERG agrees that the marketing authorisation did not specify any subtypes of PFIC,[2] and, as outlined in Section 2.1.1, clinical advice received by the ERG concurs that the mechanism of action of odevixibat is expected to be the same across any chronic cholestatic disorder with itch but some degree of bile flow (i.e. not those patients with a complete absence of BSEP protein).

2.1.3 Accumulating data among patients with PFIC4, PFIC5 and PFIC6

The company highlights some evidence from the PEDFIC2[3] study in the ECD response, which displays reductions in pruritus scores and sBA among patients with rarer subtypes PFIC3 and PFIC6 over 9-12 weeks (see Figure 1) and some evidence from the Phase 2 study[4] demonstrating a reduction in sBA over 4 weeks in patients with PFIC3 (see Figure 2; [redacted][5]).

This reduction looks smaller among the patient with PFIC6 than for patients with PFIC3 (Figure 1), however the extremely small numbers of patients with PFIC3 and PFIC6 preclude examining any differences in sBA response between these two subgroups. The company also state that clinical data will continue to be collected for patients of all PFIC subtypes in the ongoing PEDFIC2 study and the PFIC registry.

Figure 1: Changes in pruritus and sBA observed in subtypes of patients in PEDFIC2 (reproduced from company's ECD response, Figure 1)



The ERG notes that there is some evidence that patients with PFIC3 respond to odevixibat. Among the 5 patients with PFIC3 enrolled in Cohort 2 of PEDFIC2, 4 (80%) met the sBA responder definition as of the data cut-off and all had ≥94% positive pruritus assessments (defined as a scratching score of ≤1

or at least a 1 point decrease from baseline on the Albireo ObsRO instrument[3]) at the last assessment prior to data cut off.[5] The one patient with PFIC6 who enrolled in PEDFIC2 experienced reductions in pruritus and sBA levels over the course of 9-12 weeks, although the ERG notes that the reduction in sBA levels is small and it is difficult to extrapolate findings from one patient across the whole patient population. Further emergent evidence among the rarer PFIC subtypes will be useful in determining the effectiveness of odevixibat with greater precision.

[redacted]

Figure 2: [redacted]

2.2 Disutility of a stoma bag in children with PFIC

In the ECD response, the company highlights the statement in Section 4.28 of the ECD that "*The committee agreed that the disutility of living with a stoma bag was likely to be lower than both the company and ERG's preferred values, but higher than the utility derived by the company's elicitation study. It would have preferred to see analyses using alternative stoma bag disutilities.*" Furthermore, the company notes it is described in the ECD that "*the clinical experts explained that the stoma-related effect on quality of life is significant, especially in older children. This is because the disutility may be larger in them and they often refuse an external biliary diversion. The clinical expert also highlighted that stoma-related quality of life was likely to be better for someone with colorectal cancer or ulcerative colitis than for someone with a stoma bag collecting bile. This is because of problems arising from the irritant nature of bile. The patient experts highlighted that people with PFIC and carers have a very negative attitude to having a stoma bag."*

In their original submission, the company identified two sources for the disutility associated with partial external biliary diversion (PEBD). The first was in patients with ulcerative colitis (UC) which gave a utility multiplier of 0.72 and the second in patients with colorectal cancer (CC), which gave a utility multiplier of 0.945. In the ERG report, a utility multiplier of 0.833 was used, which is the average of two values in the studies identified by the company (i.e. 0.722 and 0.945).

In its response to the ECD, the company states that they consulted with three clinical experts who confirmed that the utility multiplier derived from ulcerative colitis is appropriate but likely underestimates the impact of a biliary stoma. Based on this, the company believes that the committee's preferred utility multiplier based on the average of the colorectal cancer and ulcerative colitis studies (0.833) understates the impact of PEBD and that the true value would be closer to or worse than that for ulcerative colitis (0.722). As such, the company assumes a value of 0.722 for the utility multiplier associated with PEBD in the company's base-case analyses, which results in an incremental cost-effectiveness ratio (ICER) of [redacted] per QALY using the original PAS (see Section 3).

In addition, the company also performed scenario analyses utility multiplier of [redacted] estimated from the company's vignette study (for further details, see the Appendices, which reproduce the results presented by the company in their response to ECD). Given the feedback from the committee in section 4.28 of the ECD, the ERG does not consider this estimate to be appropriate.

The ERG sought advice from the clinical experts post ECD who confirmed that the disutility due to stoma bag is likely to be similar to the disutility of ulcerative colitis. As such, the ERG is comfortable with the use of a utility multiplier of 0.722 and has used this value in the ERG preferred analyses (see Section 4).

2.3 Response criteria and dose escalation

Following discussion among NICE's clinical advisors in the Evaluation Committee meeting to clarify response criteria in clinical practice, the ECD[1] states, "*The clinical experts classed an adequate response to odevixibat as improvements in at least 2 of the 3 main PFIC outcomes: serum bile acid levels, pruritus and liver function tests. They acknowledged that a definition of response might vary among clinicians. However, they explained that the dose of odevixibat would likely be increased if little or no improvement in these outcomes was seen.*" In their ECD response, the company confirm that their own clinical advisors concur with this definition and would apply it in clinical practice to determine response to odevixibat and assess the need for dose escalation.

The ERG's clinical advisors also concur with this view, with the caveat that pruritus is the most important outcome clinically, and the one that would primarily be used to assess response. The ERG

notes that these outcomes are generally consistent with the key outcomes in the PEDFIC1[6] and PEDFIC2[3] studies, and thus the evidence is broadly reflective of prospective clinical practice in England.

2.4 PEBD as an option in the odevixibat arm

In the ECD response, the company acknowledges the statement in Section 4.22 of the ECD that "*It concluded that PEBD should have been included in both arms. It also concluded that the rates should be considered in exploratory analyses, if possible, informed by a data source that was clinically relevant to the NHS".*

In the ECD response, the company agrees in principle that there is the potential for PEBD to be used after odevixibat. The company's updated base-case analysis includes PEBD surgery in both arms and PEBD is assumed to occur at the same rate (estimated from the NAPPED study) in the non-responders to odevixibat as in the standard of care (SoC) arm.

In addition, the company also performed scenario analyses using different rates of PEBD surgery in the two arms resulting in ICERs ranging between [redacted]/QALY and [redacted]/QALY (for further details, see the Appendices, which reproduce the results presented by the company in their response to ECD). The company states that these scenario analyses are based on the clinician advice that the PEBD rates used in the model may be higher than seen in clinical practice, and that the rate of PEBD among patients who have previously received odevixibat may be lower.

As acknowledged by the company in the ECD response, "*NICE and the ERG received expert clinical advice that suggested that PEBD surgery could be offered to those who did not respond on odevixibat.*" As such, in the ERG preferred analyses, PEBD surgery was included in both arms assuming that they occur at the same rate in the non-responders to odevixibat as in the SoC arm (see Section 4).

2.5 Rate of mortality after second transplant

In response to the ECD, the company explored scenarios in which there is increased risk of mortality post liver transplant after a re-transplant. Data from Watt *et al.*[7] was used by the company to perform two scenario analyses: a) all re-transplants occur within 1 year of the initial transplant and these patients have a hazard ratio (HR) of 1.52 applied to the baseline risk; b) all re-transplants occur more than 1 year after initial transplant and the HR applied is 4.79 (see Appendices, which reproduce the results presented by the company in their response to ECD).

The ERG notes that in the company's original base case model, all re-transplants were assumed to occur within the first year and the rate of mortality was unchanged by re-transplant. Based on the revised

model submitted by the company, the ERG's understanding is that in these scenario analyses, the company adjusted the risk of death beyond one year after the original transplant to be a weighted average of the baseline hazard and that with the HR applied, weighted according to the proportion of patients not having and having a re-transplant respectively.

The ERG notes that the data from Watt et al 2010[7] is based on liver transplants that occurred from 1990-94. Furthermore, Watt et al[7] acknowledged that by 2010 re-transplantation had improved and the HRs might no longer have been relevant. In addition, the ERG found the description of the statistical analysis in Watt et al[7] incomplete and identified some inconsistency of reporting between the text and the results tables: whilst the HR of 4.79 for re-transplant beyond 1 year was statistically significant as a univariate analysis ($p<0.0001$), the HR of 1.52 for re-transplant up to 1 year was not ($p=0.12$). Therefore, only the former covariate was included in the multivariate analysis which gave an adjusted HR of 5.04 associated with re-transplant after one year. In addition, re-transplant at any time was not found to be associated with mortality after 5 years post liver transplant. For these reasons, the ERG believes that using an ongoing HR of 4.79 for mortality related to re-transplant post 1-year is not plausible.

The advice from the clinical expert to the ERG suggested that a 30% increased risk of mortality following re-transplant was expected and also thought that a HR of 4.79 was not plausible. As such, to explore the uncertainty regarding increased mortality of re-transplant, the ERG believes that the scenario analyses using a maximum HR of 1.52 assuming that the re-transplants happen within 1 year of the initial transplant is reasonable. Given the uncertainty in the data, the ERG did not include this HR in the base case analyses but explored it as part of the ERG additional scenario analyses (see Section 4).

2.6 Options to address and alleviate the cost-effectiveness uncertainties

The company states in the ECD response that they are in discussions with NICE PASLU and NHS England around commercial options that may address the cost-effectiveness uncertainties. The company states that it [redacted] The company states that [redacted]. In response to the ECD, the company also presented their base case analyses with the [redacted] that results in an ICER of [redacted] per QALY (see Section 3).

2.7 Impact of odevixibat outside of the NICE reference case

In their response to ECD, the company presented results of scenario analyses including carer productivity costs (see Appendices, which reproduce the results presented by the company in their response to ECD). Whilst the company acknowledges in the response to ECD that carer productivity

costs are outside of the NICE reference case, the company maintains that these results reflect the important impact that odevixibat may have beyond the direct health benefits for patients and should be taken into account when appraising the cost-effectiveness of odevixibat.

The company suggests, based on the results of the PICTURE study, that [redacted]. The company also notes that in the ECD, the carers explained that "*they needed to provide constant care to children with PFIC. Commonly, the demands are such that carers cannot work full time, resulting in loss of earnings and implications for career development. One carer explained that she could no longer carry on with her job as her daughter deteriorated because of the demands of juggling hospital visits and sleepless nights.*"

As described in the ERG report, there is no specific guidance reported in NICE interim Methods Guide for HSTs[8] regarding the inclusion of productivity costs whilst the NICE guide to the methods of technology appraisal[9] suggests that *"Productivity costs are not included in either the reference-case or non-reference-case analyses".* Furthermore, there is no guidance on the appropriate valuation of productivity costs).

The ERG notes that productivity and out-of-pocket expenditure are not part of the reference case and has excluded this from its preferred analyses.

3 Company's updated base case analyses

The company states that its updated base-case reflects the committee's preferred assumptions as outlined in section 4.34 of the ECD, with one exception that a utility multiplier of 0.72 was applied for the PEBD health states. The company also presented scenario analyses to explore the impact of stoma disutilites; rate of PEBD in the SoC arm and following odevixibat; rate of mortality after a second liver transplant; and productivity costs on the cost-effectiveness of odevixibat. These are reproduced in Appendix A (original PAS) and Appendix B (new proposed PAS).

Table 7 presents the company's updated base-case results with original PAS. The original PAS was a simple price discount of [redacted] on the list price for odevixibat, which was [redacted] per pack of 30 capsules containing 200 µg, 400 µg, 600 µg or 1,200 µg, respectively.

Table 1: Updated company's base-case results with original PAS

Technologies	Total costs (£)	Total LYG	Total QALYs	Inc. costs (£)	Inc. LYG	Inc. QALYs	ICER
Standard care	[redacted]	20.89	[redacted]				
Odevixibat	[redacted]	22.91	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years							

Table 2 presents the company's updated base-case results with the new proposed PAS which is a [redacted]. Note that the proposed PAS has not been formally agreed.

Table 2: Company's updated base-case results with new proposed PAS

Technologies	Total costs (£)	Total LYG	Total QALYs	Inc. costs (£)	Inc. LYG	Inc. QALYs	ICER
Standard care	[redacted]	20.89	[redacted]				
Odevixibat	[redacted]	22.91	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years							

4 Analyses undertaken by the ERG

The results of the ERG preferred analyses and scenario analyses are presented using the original PAS as well as the new proposed PAS. Note that the proposed PAS has not been formally agreed.

The ERG undertook analyses with the following changes from the base case in the ERG report

- Using a utility multiplier of 0.722 for PEBD surgery
- Including PEBD in the odevixibat arm, and assuming that it occurs at the same rate for non-responders to odevixibat as in the SoC arm

The ERG preferred base-case is now therefore the same as the new company's base-case following ECD consultation. Whilst the ERG's preferred analysis is the same as the company's base case submitted in response to the ECD, it should be noted that there remains considerable uncertainty surrounding the cost-effectiveness of odevixibat.

Table 3 shows the results of the ERGs probabilistic and deterministic results of the ERG's updated preferred analyses using the original PAS, which is a simple price discount of [redacted] on the list price for odevixibat.

Table 3: Results of the ERG's preferred analyses, original PAS

Option	Inc. QALYs	Inc. costs	ICER
ERG preferred analysis: deterministic	[redacted]	[redacted]	[redacted]
ERG preferred analysis: probabilistic	[redacted]	[redacted]	[redacted]

The ERG also undertook further additional analyses by running all the scenarios outlined in the initial ERG report. Table 4 shows the deterministic results of the ERG's additional scenario analysis using the original PAS, which include the following amendments to the ERG preferred model.

(1) Amending the proportions of patients on low doses (33%, 50% and 66%)

Within these analyses, the proportion of patients receiving low dose was amended from the current value used in the model of [redacted] to 33%, 50% and 66%, respectively representing sub-analyses 1a, 1b and 1c.

(2) Mortality of non-responders (to general population mortality)

Within this analysis, the mortality risk for non-responders (both odevixibat non-responders and PEBD non-responders) was set equal to general population mortality according to the patient's age in each model cycle.

(3) Excluding caregiver disutilities

Within this analysis, the caregiver QALYs (which were lost due to disutility of caring for patients with PFIC) were excluded from the analysis.

(4) Amending the starting age of the patients to 3 years

At the start of the model, patients were assigned an age of 3 years within this analysis rather than the starting age of 4.25 years.

(5) Excluding PEBD in the odevixibat arm

Within this analysis, it was assumed that the annual probability of PEBD in non-responders in odevixibat arm is zero.

(6) Using lower costs for PEBD surgery

Within this analysis, it was assumed that one-off costs associated with PEBD surgery were lower at £15,000 (compared to £22,119 used in the base-case model).

(7) Assuming higher annual loss of response to odevixibat

Within this analysis, the annual loss of response to odevixibat is assumed to be equal to that of PEBD (5%).

(8) Increased mortality for patients with re-transplant

Within this analysis, a HR of 1.52 was used for post-transplant mortality for patients that have been re-transplanted, assuming that the re-transplants happen within 1 year of the initial transplant. The ERG noted a slight discrepancy in the results when the ERG replicated this scenario analysis (£[redacted]/QALY) compared to the results reported by the company in their response to ECD ([redacted]/QALY).

Table 4: ERG updated additional scenario analyses following ACM1, original PAS

Option	LYGs *	QALYs	Costs	Inc. LYGs *	Inc. QALYs	Inc. costs	ICER
ERG preferred analysis							
Odevixibat	58.94	[redacted]	[redacted]	7.50	[redacted]	[redacted]	[redacted]
Standard of Care	51.44	[redacted]	[redacted]	-	-	-	-
ASA1a: Proportion of patients receiving high dose odevixibat=33%							
Odevixibat	58.94	[redacted]	[redacted]	7.50	[redacted]	[redacted]	[redacted]
Standard of Care	51.44	[redacted]	[redacted]				
ASA1b: Proportion of patients receiving high dose odevixibat=50%							
Odevixibat	58.94	[redacted]	[redacted]	7.50	[redacted]	[redacted]	[redacted]
Standard of Care	51.44	[redacted]	[redacted]				
ASA1c: Proportion of patients receiving high dose odevixibat=66%							
Odevixibat	58.94	[redacted]	[redacted]	7.50	[redacted]	[redacted]	[redacted]
Standard of Care	51.44	[redacted]	[redacted]				
ASA2: General population mortality for non-responders							
Odevixibat	59.74	[redacted]	[redacted]	7.19	[redacted]	[redacted]	[redacted]
Standard of Care	52.55	[redacted]	[redacted]				
ASA3: Excluding caregiver disutilities							
Odevixibat	58.94	[redacted]	[redacted]	7.50	[redacted]	[redacted]	[redacted]
Standard of Care	51.44	[redacted]	[redacted]				
ASA4: Start age of 3 years							
Odevixibat	59.40	[redacted]	[redacted]	7.62	[redacted]	[redacted]	[redacted]
Standard of Care	51.79	[redacted]	[redacted]				
ASA5: Excluding PEBD in odevixibat arm							
Odevixibat	57.50	[redacted]	[redacted]	6.06	[redacted]	[redacted]	[redacted]
Standard of Care	51.44	[redacted]	[redacted]				
ASA6: Assuming lower costs of PEBD							
Odevixibat	58.94	[redacted]	[redacted]	7.50	[redacted]	[redacted]	[redacted]
Standard of Care	51.44	[redacted]	[redacted]				
ASA7: Assuming higher annual loss of response to odevixibat							
Odevixibat	57.46	[redacted]	[redacted]	6.02	[redacted]	[redacted]	[redacted]
Standard of Care	51.44	[redacted]	[redacted]				
ASA8: Assuming increased mortality for patients with re-transplant							
Odevixibat	58.77	[redacted]	[redacted]	7.51	[redacted]	[redacted]	[redacted]
Standard of Care	51.26	[redacted]	[redacted]				

**Undiscounted*
ASA - additional scenario analysis; ICER - incremental cost effectiveness ratio; LYG - life years gained; PEBD - partial external biliary diversion; QALY = quality adjusted life year

Table 5 shows the results of the ERGs probabilistic and deterministic results of the ERG's updated preferred analyses with the proposed PAS ([redacted]

Table 5: Results of the ERG's preferred analyses, new proposed PAS

Option	Inc. QALYs	Inc. costs	ICER
ERG preferred analysis: deterministic	[redacted]	[redacted]	[redacted]

ERG preferred analysis: probabilistic	[redacted]	[redacted]	[redacted]

Table 6 shows the deterministic results of the ERG's additional scenario analysis with the new proposed PAS included. [redacted]. Also, the ERG noted a slight discrepancy in the results when the ERG replicated this scenario analysis (£[redacted]/QALY) compared to the results reported by the company in their response to ECD ([redacted]/QALY).

Table 6: ERG updated additional scenario analyses following ACM1, new proposed PAS

Option	LYGs *	QALYs	Costs	Inc. LYGs *	Inc. QALYs	Inc. costs	ICER
ERG preferred analysis							
Odevixibat	58.94	[redacted]	[redacted]	7.50	[redacted]	[redacted]	[redacted]
Standard of Care	51.44	[redacted]	[redacted]	-	-	-	-
ASA1a: Proportion of patients receiving high dose odevixibat=33%							
Odevixibat	58.94	[redacted]	[redacted]	7.50	[redacted]	[redacted]	[redacted]
Standard of Care	51.44	[redacted]	[redacted]	-	-	-	-
ASA1b: Proportion of patients receiving high dose odevixibat=50%							
Odevixibat	58.94	[redacted]	[redacted]	7.50	[redacted]	[redacted]	[redacted]
Standard of Care	51.44	[redacted]	[redacted]	-	-	-	-
ASA1c: Proportion of patients receiving high dose odevixibat=66%							
Odevixibat	58.94	[redacted]	[redacted]	7.50	[redacted]	[redacted]	[redacted]
Standard of Care	51.44	[redacted]	[redacted]	-	-	-	-
ASA2: General population mortality for non-responders							
Odevixibat	59.74	[redacted]	[redacted]	7.19	[redacted]	[redacted]	[redacted]
Standard of Care	52.55	[redacted]	[redacted]				
ASA3: Excluding caregiver disutilities							
Odevixibat	58.94	[redacted]	[redacted]	7.50	[redacted]	[redacted]	[redacted]
Standard of Care	51.44	[redacted]	[redacted]				
ASA4: Start age of 3 years							
Odevixibat	59.40	[redacted]	[redacted]	7.62	[redacted]	[redacted]	[redacted]
Standard of Care	51.79	[redacted]	[redacted]				
ASA5: Excluding PEBD in odevixibat arm							
Odevixibat	57.50	[redacted]	[redacted]	6.06	[redacted]	[redacted]	[redacted]
Standard of Care	51.44	[redacted]	[redacted]				
ASA6: Assuming lower costs of PEBD							
Odevixibat	58.94	[redacted]	[redacted]	7.50	[redacted]	[redacted]	[redacted]
Standard of Care	51.44	[redacted]	[redacted]				
ASA7: Assuming higher annual loss of response to odevixibat (5%)							
Odevixibat	57.46	[redacted]	[redacted]	6.02	[redacted]	[redacted]	[redacted]
Standard of Care	51.44	[redacted]	[redacted]				
ASA8: Assuming increased mortality for patients with re-transplant							
Odevixibat	58.77	[redacted]	[redacted]	7.51	[redacted]	[redacted]	[redacted]
Standard of Care	51.26	[redacted]	[redacted]				

**Undiscounted*
ASA - additional scenario analysis; ICER - incremental cost effectiveness ratio; LYG - life years gained; PEBD - partial external biliary diversion; QALY = quality adjusted life year

5 Discussion

The company responded to the ECD focussing on seven key issues that were raised in the ECD, and with a new proposed PAS (awaiting approval). Given the rarity of subtypes PFIC4, PFIC5 and PFIC6, and given the mechanism of action of odevixibat, the clinical advisors to the ERG agree that it is not unreasonable for odevixibat, if it is approved, to be approved for all subtypes of PFIC, consistent with the marketing authorisation, although uncertainty remains around the clinical effectiveness of odevixibat in rarer PFIC subtypes due to a dearth of evidence at the present time. The ERG recommends that data collection on the effectiveness of odevixibat among rarer subtypes continues through the PEDFIC2 study and through registries. The company agrees with NICE's definition for response and dose escalation, as presented in the ECD, and clinical advisors to the ERG concurs with this view, with the suggestion that pruritus response be prioritised as an outcome.

The ERG undertook analyses with the following changes from the base case in the ERG report

- Using a utility multiplier of 0.722 for PEBD surgery
- Including PEBD in the odevixibat arm, and assuming that it occurs at the same rate for non-responders to odevixibat as in the SoC arm

Based on the advice received by the ERG from the clinical experts and the feedback from the committee, the disutility due to stoma bag is likely to be similar to the disutility of ulcerative colitis. As such, the ERG agrees with the company in using a utility multiplier of 0.722 for PEBD surgery in the ERG preferred analyses. Similarly, based on the feedback from the committee, the ERG agrees with the company in the inclusion of PEBD surgery in both arms and assuming that they occur at the same rate in the non-responders to odevixibat as in the SoC arm.

The ERG preferred base-case is now therefore the same as the new company's base-case following ECD consultation, however, it should be noted that there remains considerable uncertainty surrounding the cost-effectiveness of odevixibat. The results of the ERG preferred analyses and scenario analyses are presented using the original PAS (simple price discount of [redacted] on the list price for odevixibat) as well as the new proposed PAS ([redacted].

The company also presented a number of scenario analyses in the response to the ECD. The company performed scenario analyses using different rates of PEBD surgery in the two arms, which the ERG

considers appropriate for exploring the underlying uncertainty associated with the rate of PEBD. The company also explored scenarios in which there is increased risk of mortality following a second liver transplant. The ERG believes using a HR of 1.52 assuming that the re-transplants happen within 1 year of the initial transplant seems appropriate for exploring the underlying uncertainty regarding increased mortality of re-transplant, while the scenario analysis using a HR of 4.79 assuming all re-transplants occur more than 1 year after the initial transplant is considered implausible by the ERG. However, given the uncertainty in the mortality data post re-transplant, the ERG did not include the HRs in its preferred analyses. The company also performed a scenario analysis including caregiver productivity costs, however, the ERG notes that productivity and out-of-pocket expenditure are not part of the reference case and has excluded this from its preferred analyses.

Additional exploratory analyses were also undertaken using the ERG's preferred version of the model to explore the impact of alternative values for parameters such as annual loss of response, mortality risks, impact of altering assumptions regarding drug dosage, exclusion of PEBD surgery for non-responders on odevixibat, increased mortality with re-transplantation and excluding caregiver disutilities. Using the original PAS, the ERG's additional exploratory analyses using the ERG's preferred version of the model produce ICERs which are in the range of [redacted] to [redacted]. Using the new proposed PAS, the ICERs are in the range of [redacted] to [redacted]. These exploratory analyses highlight the significant influence of the assumptions regarding odevixibat dose and inclusion of caregiver disutilities.

6 References

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Appendix A: Company's updated results with the original PAS (reproduced from the company's response to ECD)

The company states that its updated base-case reflects the committee's preferred assumptions as outlined in section 4.34 of the ECD, with one exception that a utility multiplier of 0.72 was applied for the PEBD health states. Table 7 presents the updated base-case results with original PAS.

Table 7: Updated company's base-case results with original PAS

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£) incremental (QALYs)
Standard care	[redacted]	20.89	[redacted]				
Odevixibat	[redacted]	22.91	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years							

Table 8 presents the results of the scenarios presented by the company considering different rates of PEBD using original PAS. Table 9 presents the results of the remaining scenario analyses presented by the company using original PAS.

Table 8: Company's scenario analyses considering different rates of PEBD with original PAS

		Rate of PEBD in the SoC arm			
		Base-case	50% reduction	75% reduction	90% reduction
Rate of PEBD in the odevixibat arm	Base-case	[redacted]	-	-	-
	50% reduction	[redacted]	[redacted]	-	-
	75% reduction	[redacted]	[redacted]	[redacted]	-
	90% reduction	[redacted]	[redacted]	[redacted]	[redacted]
	No PEBD	[redacted]	[redacted]	[redacted]	[redacted]

Table 9: Company's additional scenario analyses with original PAS

Scenario	Inc. costs	Inc. QALYs	ICER
Base-case	[redacted]	[redacted]	[redacted]

Committees preferred analysis (stoma utility multiplier = 0.833)	[redacted]	[redacted]	[redacted]
Stoma multiplier from the vignette study ([redacted])	[redacted]	[redacted]	[redacted]
Carer productivity costs included	[redacted]	[redacted]	[redacted]
HR of 1.52 applied to post-LT mortality	[redacted]	[redacted]	[redacted]
HR of 4.79 applied to post-LT mortality	[redacted]	[redacted]	[redacted]

Appendix B: Company's updated results with the new proposed PAS (reproduced from the company's response to ECD)

The company states that its updated base-case reflects the committee's preferred assumptions as outlined in section 4.34 of the ECD, with one exception that a utility multiplier of 0.72 was applied for the PEBD health states. Table 7 presents the updated base-case results with new proposed PAS.

Table 10: Updated base-case results with new proposed PAS

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£) incremental (QALYs)
Standard care	[redacted]	20.89	[redacted]				
Odevixibat	[redacted]	22.91	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years

Table 8 presents the results of the scenarios presented by the company considering different rates of PEBD using new proposed PAS. Table 9 presents the results of the remaining scenario analyses presented by the company using new proposed PAS.

Table 11: Scenario analyses considering different rates of PEBD with new proposed PAS

		Rate of PEBD in the SoC arm			
		Base-case	50% reduction	75% reduction*	90% reduction
Rate of PEBD in the odevixibat arm	Base-case	[redacted]	-	-	-
	50% reduction	[redacted]	[redacted]	-	-
	75% reduction	[redacted]	[redacted]	[redacted]	-
	90% reduction	[redacted]	[redacted]	[redacted]	[redacted]
	No PEBD	[redacted]	[redacted]	[redacted]	[redacted]

*The ERG noticed an error in the three ICERs included in this column when they checked the analyses. In the scenarios included in this column, a 25% reduction has been used instead of a 75% reduction in the SoC arm. The correct results should therefore be [redacted], [redacted] and [redacted], respectively.

Table 12: Additional scenario analyses with new proposed PAS

Scenario	Inc. costs	Inc. QALYs	ICER
Base-case	[redacted]	[redacted]	[redacted]
Committees preferred analysis (stoma utility multiplier = 0.833)	[redacted]	[redacted]	[redacted]
Stoma multiplier from the vignette study ([redacted])	[redacted]	[redacted]	[redacted]
Carer productivity costs included	[redacted]	[redacted]	[redacted]
HR of 1.52 applied to post-LT mortality	[redacted]	[redacted]	[redacted]
HR of 4.79 applied to post-LT mortality	[redacted]	[redacted]	[redacted]