National Institute for Health and Care Excellence

Health Technology Evaluation

Maralixibat for treating cholestatic pruritus in Alagille Syndrome ID3941
Response to stakeholder organisation comments on the draft remit and draft scope

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Comment 1: the draft remit and proposed process

Section	Stakeholder	Comments [sic]	Action
Appropriateness of an evaluation and proposed evaluation route	Genetic Alliance UK	Genetic Alliance UK understands from the Children's Liver Disease Foundation that the appraisal of Maralixibat for Alagille syndrome has been delayed due to uncertainty over the population numbers resulting in routing via the STA pathway rather than the HST pathway. Alagille syndrome is a severe condition that causes debilitating pruritus. Current treatment options are general treatments for symptom management, not specific for Alagille syndrome, and are considered to not be entirely effective. The only criteria that this technology may fail to meet for HST routing is around the prevalence and eligible population criteria. Genetic Alliance UK believes that this technology would be suitable for HST routing given the uncertainty around the population numbers (see more detail in the population section below). This would be a good case to exercise flexibility in the committee's decision as to ensure this technology is not disadvantaged from being assessed via the STA pathway rather than the HST pathway.	Thank you for your comments. This topic does not meet HST criteria and therefore continues as STA. No action is needed
	Children's Liver Disease Foundation	CLDF believe that this is a priority topic due to there being no alternative authorised treatment other than surgery and liver transplantation for some of the complex liver issues which can be a feature of the syndrome. Children	Thank you for your comments.

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		can experience a wide range of issues with this syndrome, not all relate to the liver. The issues which relate to Cholestasis - pruritus and low growth, have a significant impact on the welfare and quality of life of the child and the family who care for them. Pruritus is a common symptom and as well as severe itching, it can cause fatigue, disturbed sleep, reduced appetite, nausea and vomiting. It can affect all aspects of daily life and can be utterly debilitating. We believe that this therapy and any therapy for the liver related issues of Alagille Syndrome should be assessed through the NICE Highly Specialised Technology Appraisal. Specialist paediatric liver disease services for all children in the UK come under NHS England's Highly Specialised Commissioning Services and patients are seen in one of only three specialist paediatric liver centres in the UK (Birmingham Children's Hospital NHS Foundation Trust; King's College Hospital NHS Foundation Trust; Leeds Teaching Hospitals NHS Trust) https://www.england.nhs.uk/commissioning/wp-content/uploads/sites/12/2018/12/Highly-Specialised-Services-2018-v2.pdf All other NICE appraisals that CLDF have been involved with in the past have been through the highly specialised technology route. Paediatric liver conditions, including Alagille Syndrome, are rare conditions and as a result many professionals will not have a full understanding due to the complex and rare nature of the conditions.	This topic does not meet HST criteria and therefore continues as STA. No action is needed
	Mirum Pharmaceuticals	Yes, we agree NICE should consider this topic for appraisal. However, we believe that the topic fulfils the criteria to be evaluated through the Highly Specialised Technology (HST) programme, as evidenced in the supporting 'HST checklist – for company' document provided with this consultation comment form. ALGS is a very rare, burdensome and life-threatening disease with no currently available disease modifying treatment outside of paediatric liver transplantation. Maralixibat has clearly demonstrated efficacy to relieve	Thank you for your comments. This topic does not meet HST criteria and therefore continues as STA. No action is needed

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		patients of the burden of this disease and prevent the need for paediatric liver transplantation, in the small patient population that exists. Since the original scoping in 2021, Mirum have provided additional information where necessary to ensure the appropriate routing can be decided, based on the limited data that is available, with the goal to get patients access as quickly as possible to maralixibat and reduce the number of patients suffering from this burdensome disease. To ensure maralixibat can reach these patients as quickly as they require, with the appropriate cost-per-QALY threshold to support a technology indicated for a rare disease, the HST routing should be selected for the appraisal.	
Wording	Genetic Alliance UK	No comments.	No action needed.
	Children's Liver Disease Foundation	No comments.	No action needed.
	Mirum Pharmaceuticals	Yes.	Thank you for your comments. No action is needed.
Timing Issues	Genetic Alliance UK	Given the delays this appraisal has already faced, it should proceed as quickly as possible so that patients do not face further delays in accessing treatment.	Thank you for your comments. No action is needed.
	Children's Liver Disease Foundation	We believe this continues to be high as there has been a significant delay to possible access to this medication already and there continues to be no alternative treatment other than surgery and liver transplantation. Current therapies only reduce symptoms.	Thank you for your comments. No action is needed.
	Mirum Pharmaceuticals	High – currently there are no licensed therapies in the UK for the treatment of ALGS, with liver transplantation being the only treatment option available that may alleviate symptoms.	Thank you for your comments.

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		Due to the invasive nature of surgical treatment options, the burden of long-term immunosuppressive therapy post-transplant, and patients' lifelong morbidity and mortality, there remains a high unmet medical need for an early and easily reversible pharmacological treatment in patients with ALGS that is safe and efficacious in easing disease burden (Sanchez et al., 2021). The successful rapid evaluation of the technology is critical for children who otherwise would continue to suffer from debilitating symptoms, poor quality of life for both patient and carer, as well as a 60% chance of liver transplantation or death by age 18 (Vandriel et al., 2023). Patients require a treatment that is ready to be commercialised immediately, requires no further regulatory approval, and is supported by robust trial data that is published in reputable journals. The topic fulfils the criteria to be evaluated through the Highly Specialised Technology (HST) programme – as evidenced in the 'HST checklist – for company' document, and any delay caused by incorrect scoping of the technology, will impact on patients that desperately need treatment for this disease, before a liver transplant is required.	This topic does not meet HST criteria and therefore continues as STA. No action is needed
Additional comments on the draft remit	Genetic Alliance UK	No comments.	No action is needed
	Children's Liver Disease Foundation	No comments.	No action is needed
	Mirum Pharmaceuticals	No.	No action is needed

Comment 2: the draft scope

Section	Consultee/ Commentator	Comments [sic]	Action
Background information	Genetic Alliance UK	The itching caused by this condition is not just debilitating for the affected individual; family members, parents and carers are also impacted. Parents and carers also have their sleep disturbed while trying to care for their child, relationships with family and friends can become strained which in turn leads to isolation and loneliness. The quality of life of the whole family is impacted, not just the affected individual.	Thank you for your comments. No action is needed.
	Children's Liver Disease Foundation	Accurate.	No action is needed.
	Mirum Pharmaceuticals	We believe the current description does not accurately depict the severity of the disease, nor describe the unmet need completely. Description should also include: *Alagille Syndrome (ALGS) is a serious, rare, genetic, progressive, life-threatening and complex multisystem disease that presents in childhood with a range of clinical manifestations, in which liver involvement can lead to end-stage liver disease.* *ALGS-associated cholestatic liver disease presents with persistent cholestasis that accounts for liver transplantation in 72% of patients* (Vandriel et al., 2023)*, the most common complication of which is debilitating and intractable pruritus. Pruritus is evidenced in 74% of patients at any point in time* (Vandriel et al., 2023)*, with the first symptoms presenting between 6 to 14 months after birth* (Kamath et al., 2018)*. Debilitating pruritus is among the most severe consequence of any chronic liver disease, causing self-mutilation, skin lesions and extensive scarring, disruption of sleep and school activities, and has a negative impact on physical and psychosocial health* (Elisofon et al., 2010)*, and QoL overall* (Kamath et al., 2015)*. Caregiver burden is significant, and caring for a child with ALGS can impose associated stress and economic burden on parents and caregivers* (Kamath et al., 2018)*.*	Thank you for your comments. Additional information about xanthomas was added. The section has also been updated in light of the comment but reflecting the current knowledge on incidence of Alagille syndrome. This topic does not meet HST criteria and therefore continues as STA.

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		Other important manifestations of cholestasis in ALGS include disfiguring xanthomas, sleep disturbances, chronic debilitating fatigue, and failure to thrive (i.e., insufficient growth) (Kamath et al., 2020a, 2010; Kronsten et al., 2013)*. Xanthomas (fatty deposits on the extensor surfaces) affect 30–42% of patients and usually appear at a median age of 20–48 months. In patients with a native liver, the presence of xanthomas is associated with a worse 10-year survival rate than those without* (Kamath et al., 2018; Lykavieris et al., 2001)*. The prevalence of growth impairment typically ranges between 50–87%* (Kamath et al., 2018)*. Collectively, these severe cholestatic symptoms and sequelae greatly impact HRQOL to patients and families.* The incidence paragraph in the 'Background' is not accurate, following evidence put forward to NICE by the Company through the last appeal process, *[information marked confidential by company has been removed].* We suggest amending the text to reflect or include the following: *"The incidence referenced in Ayoub and Kamath., 2020, refers solely to positive JAG1 or NOTCH2 mutations, which are hallmark mutations of ALGS. However, of those patients with positive mutations, "47% did not meet clinical criteria (25 out of 53)" and two of these individuals had no features consistent with ALGS at all"* (Kamath et al., 2003)*. [information marked confidential by company has been removed].* There should also be a clarification statement added after the above, that states*: "The incidence at birth is higher than the eligible patient population that would likely receive maralixibat, which will only be diagnosed patients who present with cholestatic pruritus."* The final paragraph in the 'Background' is not aligned with current literature, nor is it aligned with clinician opinion following our ratification of the unmet need in Alagille syndrome. We suggest replacing with the below:	

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		Currently there are no approved pharmacological therapies for the treatment of cholestasis in ALGS (Kriegermeier and Green, 2020) that are currently available to the NHS. Off-label, best supportive care offers limited symptomatic relief, with a suboptimal safety profile (Kriegermeier and Green, 2020). Off-label treatments to reduce pruritus may include ursodeoxycholic acid, cholestyramine, rifampicin, naltrexone and antihistamines such as chlorphenamine (Ayoub and Kamath, 2020)*. Nutritional supplements and high-calorie diets are important for many people with Alagille Syndrome, because of the difficulties cholestasis causes with absorbing fats and nutrients. If Alagille Syndrome does not respond to drug and dietary therapies, partial biliary diversion is unlikely to be carried out in current UK clinical practice [information marked confidential by company has been removed].* *Liver transplantation is the only effective treatment for the underlying liver disease. Only 40.3% of patients will survive to 18 years of age with their native liver* (Vandriel et al., 2023)*.The severe cholestasis, characterized predominantly by intractable pruritus, as well as the chronic burden of the disease manifesting in many additional symptoms, results in 59% of children with ALGS receiving a liver transplant or dying before the age of 5 years* (Kamath et al., 2020b; Vandriel et al., 2020)*, by the age of 18 years, 66% of patients will have experienced ≥1 of either clinically evidence portal hypertension (CEPH), liver transplantation or death* (Vandriel et al., 2023)*. Liver transplantation is accompanied by the risk of infection, subsequent graft failure and re-transplantation* (Miloh et al., 2017)*. Additionally, long-term immunosuppressive medication is required, which predisposes patients to chronic kidney injury, diabetes, and increased cancer risk, as well as infection* (Cuenca and Yeh, 2019; Miloh et al., 2017)*.*	

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Population	Genetic Alliance UK	The population number stated in the draft scope provides a very wide ranging estimate. We have been informed by the Children's Liver Disease Foundation that they have approximately 150 members in their database with Alagille syndrome. The scope states that approximately 80% of people with Alagille syndrome will experience pruritus, therefore the eligible population for this treatment is likely to be even lower. Although this is not a comprehensive picture of the exact prevalence in England, this suggests that the actual population of people living with Alagille syndrome is on the lower end of the estimated range. As this technology has been routed through an STA rather than HST pathway, its evaluation may be disadvantaged by the evidence constraints of smaller population numbers therefore this would be a good case for the committee to exercise flexibility in their decision making.	Thank you for your comments. The incidence paragraph has been updated to reflect current knowledge. This topic does not meet HST criteria and therefore continues as STA.
	Children's Liver Disease Foundation	We recognise that the incidence and prevalence of Alagille Syndrome is uncertain because the clinical presentation can be very variable and therefore estimations are given within the scope. From our perspective as a Children's Charity supporting those up to age 25 in the UK with liver disease, the numbers of children/young people in our patient database with Alagille's Syndrome is 4% of our total liver disease paediatric patient numbers. We appreciate that we will not be known to all Alagille's children/young people across the UK, but this shows that our Alagille's population is small compared to other conditions.	Thank you for your comments. No action is needed.
	Mirum Pharmaceuticals	No, the population should reflect the MHRA restricted population. Following EMA approval on 9 Dec 2022 Mirum completed the reliance procedure with the MHRA for a more restricted population, compared to that initially submitted for the NICE scope. MHRA granted a Marketing Authorisation for Livmarli on 10-Feb-2023 for the following indication: *"Livmarli is indicated for the treatment of cholestatic pruritus in patients with Alagille syndrome (ALGS) 2 months of age and older".*	Thank you for your comments. The scope reflects the MA of maralixibat. No action is needed.

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Subgroups	Genetic Alliance UK	Not all individuals with Alagille syndrome will experience pruritus.	Thank you for your comments. No action is needed.
	Children's Liver Disease Foundation	No comments.	No action is needed.
	Mirum Pharmaceuticals	There are currently no sub-groups noted that show benefit compared to the label population.	Thank you for your comments. No action is needed.
Comparators	Genetic Alliance UK	It is important to note that the other treatment options available are general treatments that try to manage symptoms with little efficacy. This treatment targets the bile flow issue which is the cause of many symptoms.	Thank you for your comments. No action is needed.
	Children's Liver Disease Foundation	No comments.	No action is needed.
	Mirum Pharmaceuticals	To our knowledge, the comparators listed are correct and all have been included. As is already mentioned in the scope, off-label therapies include rifampicin, bile salt-binding agents (cholestyramine), opioid antagonists, and selective serotonin re-uptake inhibitors (SSRI) (Ayoub and Kamath, 2020).	Thank you for your comments. No action is needed.
Outcomes	Genetic Alliance UK	No comments.	No action is needed.
	Children's Liver Disease Foundation	All - but health-related quality of life (for patients and carers) benefits would be from our perspective greatest. The impact of pruritis cannot be overstated. It is utterly debilitating and can affect all aspects of the child's life, episodes of	Thank you for your comments.

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		pruritis can be extreme and lead to scratching to the point where the child bleeds which have been described by patients as having an itch sometimes all over the body that simply cannot be scratched. The effect of this is not just physical; often it causes disruption to sleep and the ability to take part in everyday activities. This can have a knock-on effect on education, peer relationships and the ability to take part in normal day to day activities. Parenting a child with a severe pruritis episode is incredibly hard and can impact all aspects of family life.	No action is needed.
	Mirum Pharmaceuticals	Yes, outcomes are appropriate and will capture the most important benefits of the technology. The only addition to the existing list should be *change in xanthomas.*	Thank you for your comments. Additional information about xanthomas was added.
Equality	Genetic Alliance UK	No comments.	No action is needed.
	Children's Liver Disease Foundation	No comments.	No action is needed.
	Mirum Pharmaceuticals	No equality considerations to note assuming NICE assesses maralixibat through the route that allows the technology to be available for all suitable ALGS patients. However, should maralixibat be assessed under the STA route rather than HST, NICE will be assessing maralixibat on a route that fail due to the cost-per-QALY of the technology. The HST route has been developed to support technologies that are indicated for very rare indications, allowing a higher cost per QALY threshold, faster assessment timescale and a wider understanding of the uncertainty of some evidence presented, given the rarity and burden of the indication.	Thank you for your comments. This topic does not meet HST criteria and therefore continues as STA. No action is needed

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		Paediatric patients with ALGS require a licensed technology immediately that will prevent liver transplantation and/or early death from the disease. The proposed STA routing risks a continuation in the lack of treatment available and a continued burden on patients, caregivers and the healthcare system. Patients with analogous indications, such as PFIC (progressive familial intrahepatic cholestasis), already have access to treatment, such as odevixibat, that may reduce the number of liver transplantations or early deaths. Such treatments have been assessed through the HST route, which could lead to inequality for patients with ALGS, an analogous indication to PFIC, that may be prevented access to maralixibat on a basis of incorrect routing.	
Other considerations	Genetic Alliance UK	This technology is being assessed as a joint scoping with another technology for the same condition. It is important to note that having multiple treatment options for the same condition improves patient care and outcomes. Our current understanding as to why some people respond better to some medications than others is still developing therefore having multiple options means that patients can find the best treatment option for them. As these two medicines have a similar mode of action, it is likely that patients would not be on both medications at the same time therefore approving both wouldn't incur significant additional costs to the NHS (provided they are priced similarly).	Thank you for your comments. No action is needed
	Children's Liver Disease Foundation	No comments.	No action is needed
	Mirum Pharmaceuticals	No other considerations to note.	No action is needed
Questions for consultation	Genetic Alliance UK	No comments.	No action is needed

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	Children's Liver Disease Foundation	As stated above: We believe that this therapy and any therapy for Alagille Syndrome should be assessed through the NICE Highly Specialised Technology Appraisal. Specialist paediatric liver disease service comes under NHS England's Highly Specialised Commissioning Services and patients are seen in one of only three specialist paediatric liver centres in the UK (Birmingham Children's Hospital NHS Foundation Trust; King's College Hospital NHS Foundation Trust; Leeds Teaching Hospitals NHS Trust). https://www.england.nhs.uk/commissioning/wp-content/uploads/sites/12/2018/12/Highly-Specialised-Services-2018-v2.pdf All other NICE appraisals that CLDF have been involved with for children with liver disease in the past have been through the highly specialised technology route. Paediatric liver conditions, including Alagille Syndrome, are rare conditions and as a result many professionals will not have a full understanding due to the complex and rare nature of the conditions. There is a very small pool of consultants working in this area nationally.	Thank you for your comments. This topic does not meet HST criteria and therefore continues as STA. No action is needed.
	Mirum Pharmaceuticals	**Q1. Is the population defined appropriately in the scope?** Population should reflect the approved MHRA reliance procedure restricted population: *"treatment of cholestatic pruritus in ALGS patients for 2 months and older".* **Q2. How many people are born with Alagille Syndrome in England each year?** • There are **estimated to be between 9-13 patients born with Alagille syndrome in England each year**. • There is no published literature on the incidence of Alagille syndrome (ALGS) in England. There are three key published estimates of incidence at birth for ALGS. The estimates range from 1 in 30,000 to 1 in 100,000 (Diaz-	

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		Frias and Kondamudi, 2021; Kamath et al., 2003; Leonard et al., 2014; MedLine Genetics, 2021). • However, 1 in 30,000, which comes from the Kamath et al. 2003 paper, should not be utilised as a valid estimate of incidence, *[information marked confidential by company has been removed].* The incidence referenced in this paper refers solely to positive JAG1 or NOTCH2 mutations, which are hallmark mutations of ALGS, however of those patients with positive mutations, "*47% did not meet clinical criteria (25 out of 53)" and two of these individuals had no features consistent with ALGS at all*" (Kamath et al., 2003). *[Information marked confidential by company has been removed]* Considering the above incidence calculation, *[information marked confidential by company has been removed].* **Q3. There is a range of incidence estimates for Alagille Syndrome reported in the literature, which estimate reflects the incidence of Alagille Syndrome in England more closely?** • *[information marked confidential by company has been removed].* • As outlined above, the three key published estimates of incidence and prevalence range from 1 in 30,000 to 1 in 100,000 (Diaz-Frias and Kondamudi, 2021; Kamath et al., 2003; Leonard et al., 2014; MedLine Genetics, 2021). However, 1 in 30,000 has been demonstrated to be inaccurate *[information marked confidential by company has been removed]* and does not represent the ALGS patient population that would be diagnosed with ALGS, let alone the ALGS population that would require or receive medical attention. As outlined above, the incidence referenced in this paper refers solely to positive JAG1 or NOTCH2 mutations, which are hallmark	

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		mutations of ALGS, however of those patients with positive mutations, "*47% did not meet clinical criteria (25 out of 53)" and two of these individuals had no features consistent with ALGS at all*" (Kamath et al., 2003). *[Information marked confidential by company has been removed]*. Considering the above logical calculation steps, in the absence of accurate and robust incidence data for England, the **incidence estimate that reflects the** *[Information marked confidential by company has been removed]* (MedLine Genetics, 2021). • However, it is important to note that this is a conservative estimation of the incidence. The above incidence calculation, although more accurate than the original 1 in 30,000, does not account for patients with ALGS at birth who would be eligible for treatment with maralixibat. Patients born with ALGS would need to show evidence of cholestatic pruritus, of which occurs in 74% of patients (Vandriel et al., 2023), to be eligible for treatment with maralixibat following MHRA label change to "*treatment of cholestatic pruritus in ALGS patients for 2 months and older". [Information marked confidential by company has been removed]* given by the National Library of Medicine as part of the National Institute of Health in the United States (MedLine Genetics, 2021). To further add to the conservative estimation, it is important also to note that the 1 in 100,000 estimate presented in the literature (Diaz-Frias and Kondamudi, 2021) is *[information marked confidential by company has been removed]*. An incidence lower than *[information marked confidential by company has been removed]* has also been confirmed by several leading clinicians in ALGS in the UK, as per company documentation provided and ratification	

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		with UK clinicians on this estimate should be achieved during the scoping workshop if uncertainty still remains. • **Neonatal cholestasis related to Alagille Syndrome** **Q4. Among people with Alagille Syndrome in England, how many of them present with neonatal cholestasis, and how many of them present with non-neonatal cholestasis?** • There are estimated to be **85% of patients that present with neonatal cholestasis**. Neonatal cholestasis is generally defined as conjugated hyperbilirubinemia that occurs in the new born period (first 28 days) or shortly thereafter (i.e., within the first three months of life). • There is no specific published literature in ALGS on the number of patients that present cholestasis later in life (non-neonatal cholestasis). Expert opinion in the UK indicated that patients with ALGS with liver involvement always present with cholestasis early on (first months of life). The concept of non-neonatal cholestasis in ALGS with liver involvement does not exist in clinical practice. In addition, as confirmed by *[information marked confidential by company has been removed]*, the number of patients that present with cholestasis outside of neonatal that presents with uncontrolled pruritus that would indicate liver transplantation, is negligible. The clinicians are *[information marked confidential by company has been removed]*. Considering the aforementioned, the clarification of non-neonatal cholestasis should not be considered relevant for discussions regarding the eligible patient population for treatment with maralixibat. • Accordingly, the Global Alagille Alliance (GALA) study, an international cohort of 1,433 ALGS patients, *[information marked confidential by company has been removed]*, estimates that 85% of patients present with neonatal	

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		cholestasis (Vandriel et al., 2023), the remaining population being constituted by ALGS patients with no liver involvement or missing data. **Q5. Among people with neonatal or non-neonatal cholestasis related to Alagille Syndrome in England, how many of them would have had a liver transplant by age 18, respectively?** • For patients **presenting with neonatal cholestasis, 50.4% would have a liver transplant by age 18.** The number of patients that have had a liver transplant by age 18 for non-neonatal cholestasis is not clearly defined in published literature. • There is no specific published literature on the number of patients that present with neonatal cholestasis, nor non-neonatal cholestasis, in England. • The Global Alagille Alliance (GALA) study, an international cohort of 1,433 ALGS patients, including 44 patients from two of the three UK NHS specialist centres, **estimates that 50.4% of patients presenting with neonatal cholestasis will receive at liver transplant by age 18** (Vandriel et al., 2023). When trying to identify other studies that defined patients that were non-neonatal, a multicentre observational study followed 293 ALGS patients between 2007 to 2018, all of which presented with cholestasis and were over 2 weeks old (mean age of 5 years) (Kamath et al., 2020b). At 18.5 years, transplant-free survival was estimated to be 24% of patients (70 patients)(Kamath et al., 2020b). However, it is important to note that while patients were over 2 weeks old, there is no clarification that cholestasis was diagnosed after this point, meaning it is likely many patients would have had neonatal cholestasis in this cohort. In addition, the study cohort was US	

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		based, which is not representative of the UK patient population. For these reasons, the study was not deemed suitable to represent non-neonatal patients. • **Cholestatic pruritus related to Alagille Syndrome** **Q6. Maralixibat is indicated for treating cholestatic pruritus in patients with Alagille syndrome, how many people with Alagille Syndrome are living with cholestatic pruritus in England?** • • It is estimated that *[information marked confidential by company has been removed].* Following additional research and collaboration with key authors and clinicians in the field of Alagille syndrome (ALGS), an incidence has been determined that is fitting with clinician opinion *[information marked confidential by company has been removed]*. This has allowed a clearer and up to date calculation of the patient numbers of ALGS in England, for the MHRA approved label indication, for treatment with maralixibat. • In addition to the incidence being amended, there has since been a key publication released from the GALA study, an international cohort of 1,433 ALGS patients, *[information marked confidential by company has been removed]* (Vandriel et al., 2023). This has allowed accurate information to be obtained on the natural history cholestasis, pruritus, liver transplantation and mortality in ALGS patients, over a large population group over a long time period.	

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		• The calculation below has been ratified by the leading ALGS clinicians in the UK, and validated *[information marked confidential by company has been removed]*. • Table 1 contains a summary of the eligible patient number per step. The calculation steps have then been broken out below. **Table 1.** *[information marked confidential by company has been removed]* **Step 1 – incidence is** *[information marked confidential by company has been removed]* • The three key published estimates of incidence and prevalence range from 1 in 30,000 to 1 in 100,000 (Diaz-Frias and Kondamudi, 2021; Kamath et al., 2003; Leonard et al., 2014; MedLine Genetics, 2021). However, 1 in 30,000 has been demonstrated to be inaccurate *[information marked confidential by company has been removed]* and does not represent the ALGS patient population that would be diagnosed with ALGS, nor the ALGS population that would require or receive medical attention. As outlined above, the incidence referenced in this paper refers solely to positive JAG1 or NOTCH2 mutations, which are hallmark mutations of ALGS, however of those patients with positive mutations, "*47% did not meet clinical criteria (25 out of 53)" and two of these individuals had no features consistent with ALGS at all*" (Kamath et al., 2003). To make a clinical diagnosis of ALGS, a patient must present with at least 3 of 7 phenotypic criteria, as genetic confirmation does not constitute criteria for diagnosis of liver disease associated with ALGS (Kamath et al., 2003), nor for treatment decisions confirmed by paediatric hepatologists.	

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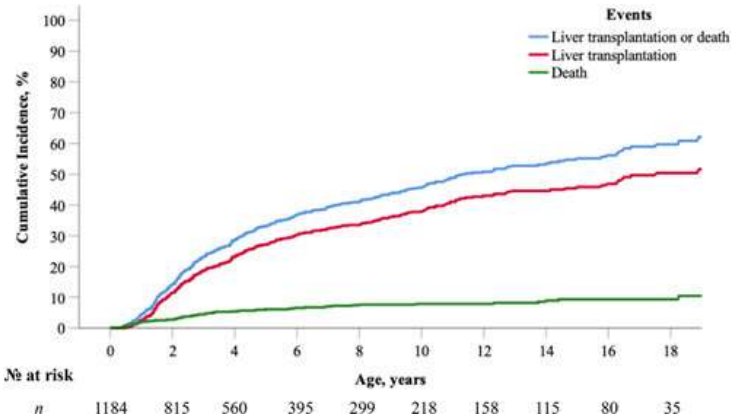
		• This means that based on the proportion of subjects with no clinical diagnosis, *[information marked confidential by company has been removed].* **Step 2 – individuals with ALGS below the age of 18 in England** There are 595,948 births in England (Office for National Statistics, 2021). Utilising *[information marked confidential by company has been removed]*, then multiplying by 18, it can be determined that there should be *[information marked confidential by company has been removed]* **with ALGS below the age of 18 in England.** **Step 3 – removing patient deaths from ALGS in patients below the age of 18** The Global Alagille Alliance (GALA) study (Vandriel et al., 2023), an international cohort of 1,433 ALGS patients *[information marked confidential by company has been removed].* The study captured cumulative incidence of native liver survival (NLS) in the presence of competing events (liver transplantation or death) in children with ALGS (**Figure 2**), which allows mortality and liver transplantation within 18 years to be determined.	

Figure 1. Cumulative incidence of NLS in GALA (Vandriel et al., 2023)



Based on the GALA data, risk of death without transplantation was 9.3% at 18 years; however, in order to account for deaths occurring over time, an integration-based method is needed. Based on the GALA data in Figure 1, the area underneath the curve is obtained by applying an integration based on mortality rates for 5, 10 and 18 years, which is then divided by the total years (18). With the assumption that no patient died before 6 months, *[information marked confidential by company has been removed]*. Therefore, *[information marked confidential by company has been removed].*

Step 4 – removing patients 2 months old and younger, to fit with the label indication

To calculate the number of patients 2 months old and younger, calculate the total months in 18 years, divided by 2 = (18*12)/2 = 108. Then divide this by the total patient number (*[information marked confidential by company has been removed]*), which gives *[information marked confidential by company has been removed]***.**

		Step 5 – removing patients without pruritus, as per the label indication • In the GALA data, **74% of patients had pruritus at some point during the study** (Vandriel et al., 2023). A very conservative assumption would be that all 74% of patients are permanently eligible, and that all with pruritus present would require treatment, regardless of the severity, meaning 74% of patients would be eligible for treatment with maralixibat. *[Information marked confidential by company has been removed]***.** This is a conservative assumption, as discussed with *[information marked confidential by company has been removed]* of pruritus patients seen in clinic present with mild pruritus that is manageable for the patient and would not require treatment and not indicate a need for transplantation. **Q7. If recommended, would all patients with Alagille Syndrome and cholestatic pruritus be eligible for maralixibat?** • It is estimated that there are *[information marked confidential by company has been removed]* **with Alagille syndrome living with treatable cholestatic pruritus in England, that would be eligible for treatment with maralixibat.** Following additional research and collaboration with key authors and clinicians in the field of Alagille syndrome (ALGS), an incidence has been determined that is fitting with clinician opinion and is also contributed by the author of the previously outdated incidence. This has allowed a clearer and up to date calculation of the patient numbers of ALGS in England, for the MHRA approved label indication, for treatment with maralixibat. • In addition to the incidence being amended, there has since been a key publication released from the GALA study, an international cohort of 1,433	

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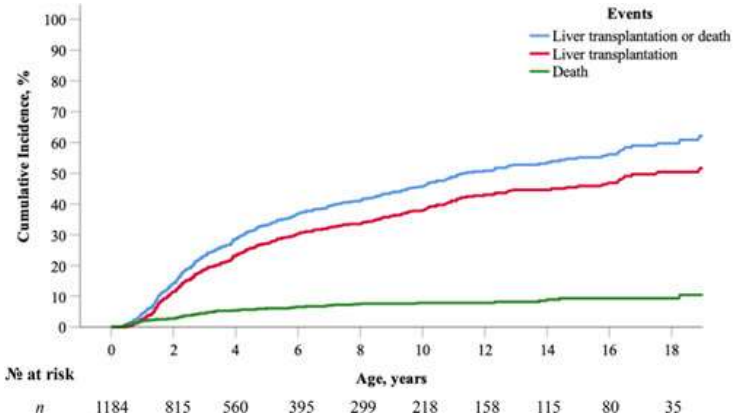
		ALGS patients, *[information marked confidential by company has been removed]* (Vandriel et al., 2023). This has allowed accurate information to be obtained on the natural history cholestasis, pruritus, liver transplantation and mortality in ALGS patients, over a large population group over a long time period. • The calculation below has been ratified by the leading ALGS clinicians in the UK, and validated by other leading clinicians *[information marked confidential by company has been removed]*. • The calculation below included conservative assumptions, including: patients presenting with mild pruritus would still receive treatment, all patients over the age of 18 years would not require liver transplantation, and all patients will be symptomatic for their whole life. Considering these assumptions, this is likely and overestimation of the true patient population. *[Information marked confidential by company has been removed].* • Table 2. *[information marked confidential by company has been removed]* contains a summary of the eligible patient number per step. The calculation steps have then been broken out below. The steps follow those shown in the answer to question 6, however include additional steps 6, 7 and 8 to account for patients that would be transplanted in childhood and conservatively in adulthood. **Table 2.** *[information marked confidential by company has been removed]*	

		Step 1 – incidence is *[information marked confidential by company has been removed]* • The three key published estimates of incidence and prevalence range from 1 in 30,000 to 1 in 100,000 (Diaz-Frias and Kondamudi, 2021; Kamath et al., 2003; Leonard et al., 2014; MedLine Genetics, 2021). However, 1 in 30,000 has been demonstrated to be inaccurate *[information marked confidential by company has been removed]* and does not represent the ALGS patient population that would be diagnosed with ALGS, nor the ALGS population that would require or receive medical attention. As outlined above, the incidence referenced in this paper refers solely to positive JAG1 or NOTCH2 mutations, which are hallmark mutations of ALGS, however of those patients with positive mutations, "*47% did not meet clinical criteria (25 out of 53)" and two of these individuals had no features consistent with ALGS at all*" (Kamath et al., 2003). To make a clinical diagnosis of ALGS, a patient must present with at least 3 of 7 phenotypic criteria , as genetic confirmation does not constitute criteria for diagnosis of liver disease associated with ALGS (Kamath et al., 2003), nor for treatment decisions confirmed by paediatric hepatologists. • This means that based on the proportion of subjects with no clinical diagnosis, the true incidence at birth for patients who presented with treatable ALGS would be *[information marked confidential by company has been removed].* **Step 2 – individuals with ALGS below the age of 18 in England** There are 595,948 births in England (Office for National Statistics, 2021). Utilising the incidence ratio *[information marked confidential by company has been removed]*, then multiplying by 18, it can be determined that there should be *[information marked confidential by company has been removed]* **individuals with ALGS below the age of 18 in England.**	

		Step 3 – removing patient deaths from ALGS in patients below the age of 18 The Global Alagille Alliance (GALA) study (Vandriel et al., 2023), an international cohort of 1,433 ALGS patients *[information marked confidential by company has been removed]*. The study captured cumulative incidence of native liver survival (NLS) in the presence of competing events (liver transplantation or death) in children with ALGS (Figure 1), which allows mortality and liver transplantation within 18 years to be determined. **Figure 2. Cumulative incidence of NLS in GALA (Vandriel et al., 2023)**  Based on the GALA data, risk of death without transplantation was 9.3% at 18 years; however, in order to account for deaths occurring over time, an integration-based method is needed. Based on the GALA data in Figure 1, the area underneath the curve is obtained by applying an integration based on mortality rates for 5, 10 and 18 years, which is then divided by the total years (18). With the assumption that no patient died before 6 months, then the estimated mortality of patients is calculated *[information marked confidential by company has been removed]*.	

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		Step 4 – removing patients 2 months old and younger, to fit with the label indication To calculate the number of patients 2 months old and younger, calculate the total months in 18 years, divided by 2 = (18*12)/2 = 108. Then divide this by the total patient number *[information marked confidential by company has been removed]***.** **Step 5 – removing patients without pruritus, as per the label indication** • In the GALA data, **74% of patients had pruritus at some point during the study** (Vandriel et al., 2023). A very conservative assumption would be that all 74% of patients are permanently eligible, and that all with pruritus present would require treatment, regardless of the severity, meaning 74% of patients would be eligible for treatment with maralixibat. *[Information marked confidential by company has been removed].* This is a conservative assumption, as discussed with *[information marked confidential by company has been removed]* of pruritus patients seen in clinic present with mild pruritus that is manageable for the patient and would not require treatment and not indicate a need for transplantation. **Step 6 – removing patients that received a liver transplant due to cholestasis** • Once patients undergo liver transplant, the burden of pruritus disappears, hence patients would need to be removed from the eligible population for	

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		maralixibat. For this reason, the rates of transplant over time are taken from the GALA data, where 50.4% of patients at 18 years received a transplantation. The data shows that 72% of transplants were caused by cholestasis (including intractable pruritus, xanthomas, etc) (Vandriel et al., 2023). Therefore, 72% of the cumulative observed transplants are removed from the patient population (which equates to 72%*50.4% = 36% of the initial population). *[Information marked confidential by company has been removed].* This is a conservative estimation as it, first, assumes that every patient that has had cholestasis has had it from 2 months and it is permanent over their lifetime, and second, that only patients that are transplanted due to cholestasis are removed from the total population. • Taking the transplanted individuals from the total number of patients in Step 5, *[information marked confidential by company has been removed]*. **Step 7 – addition of patients that remain at risk at the age of 18 and up to 65 years** • At age 18, of the 74% originally at risk with pruritus, 36% of the original patient group will have been transplanted, and 9% will have died (Vandriel et al., 2023). By subtracting the percentage of those transplanted and those dead from the original at risk *[information marked confidential by company has been removed].* As ratified by paediatric UK clinicians, a very conservative assumption is that all patients will be permanently symptomatic and that no patients will be transplanted over the age of 18. Another assumption, that has been validated by a lead adult hepatologist treating ALGS patients, is that the diagnosis of ALGS in adults in negligible.	

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		• With the aforementioned assumptions *[information marked confidential by company has been removed].* To estimate how many adult patients would be therefore eligible, calculate those born each year *[information marked confidential by company has been removed].* • As per the assumptions mentioned, the above number is very likely an overestimate. In-fact, the burden of uncontrollable pruritus in adults is extremely low, as evidenced by the lack of literature available and the fact that majority of ALGS patients undergo liver transplant by the age of 18. In addition, we have seen that the highest percentage of pruritus occurs early in childhood, and declines with age (Kamath et al., 2020b). There are very few new patients entering in clinical practice as adults. **Step 8 – total patient eligible patient population** • Combining the total eligible patient number in Step 6, with the total eligible patients beyond 18 years in Step 7, *[information marked confidential by company has been removed]***.** • It is important to note that the total number calculated above is an overestimation of the true figure, considering the two assumptions made; there is a consistency of symptoms over a patient life and that there are no further transplantations over the age of 18 years.	

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		Q8. Among people with cholestatic pruritus related to Alagille Syndrome in England, how many of them would have had a liver transplant by age 18? As per the literature available, the **proportion transplanted by age 18 could is as high as 59.7%.** There is no specific published literature on the number of patients with cholestatic pruritus related ALGS in England that would have had a liver transplant by age 18. • The Global Alagille Alliance (GALA) study, an international cohort of 1,433 ALGS patients, *[information marked confidential by company has been removed]* **estimates native liver survival (NLS) to be 40.3% at 18 years of age** (Vandriel et al., 2023). The proportion of patients receiving a liver transplant by age 18 is therefore as high as 59.7%, however it is important to consider that patients that died by age 18 years are also included within the 59.7%, hence the proportion is given as a maximum. **Treatment pathway and comparator** **Q9. Where do you consider maralixibat will fit into the existing care pathway for cholestatic pruritus related to Alagille Syndrome?** Maralixibat will be prescribed to patients following diagnosis of Alagille syndrome for eligible patients presenting with cholestatic pruritus over the age of 2 months, that have not yet had a liver transplantation. **Q10. If recommended, would maralixibat replace liver transplant in the NHS? If maralixibat is not going to completely remove the need for liver**	

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		transplant, how many patients with cholestatic pruritus and Alagille Syndrome would still need liver transplant in the NHS? The goal of maralixibat is to reduce the number of patients that would require a liver transplant. Maralixibat may not completely remove the need for liver transplant in all patients as not all patients respond equally to maralixibat. Patients may also require a liver transplantation due to other manifestations of Alagille syndrome that do not relate directly to pruritus and cholestasis, which maralixibat will not prevent against necessarily. However, it is anticipated that all eligible patients should be treated with maralixibat with the aim to demonstrate clinical efficacy in some capacity in all patients. Patients not showing clinical efficacy will be taken off of maralixibat, which will be demonstrated in the cost-effectiveness model by a stopping rule and contribute positively to the cost of the product to the NHS. To demonstrate how many patients would benefit from maralixibat compared to a natural history cohort, a real-world evidence analysis was conducted using the Global Alagille Alliance (GALA) registry - an international cohort of 1,433 ALGS patients, *[information marked confidential by company has been removed]*, compared with a combined maralixibat cohort of 84 patients, treated for up to 6 years (Hansen, BE et al., 2021). The analysis measured clinical events, defined as: liver transplant, biliary diversion surgery, decomposition event or death. The 6-year analysis demonstrated that there was a 70% reduction in clinical outcomes in the maralixibat cohort compared with the natural history cohort (Hansen, BE et al., 2021). *[Information marked confidential by company has been removed]*, as per the calculation in Step 6 in the answer to question 7 above, *[information marked confidential by company has been removed].*	

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		Therefore, it is estimated that 70% of the transplanted patient population would not receive a transplant if maralixibat was recommended for use in UK clinical practice, *[information marked confidential by company has been removed].* There is uncertainty within the calculation, related to the proportion of clinical events that are liver transplantation in the study. In addition, the calculation may be too conservative based upon the fact that patients are not eligible for maralixibat until the age of 2 months. **Q11. Could treatment with maralixibat continue in people aged over 18 years in the NHS?** Yes. **Q12. Would maralixibat be a candidate for managed access?** Yes **Q13. Which treatments are considered to be established clinical practice in the NHS for cholestatic pruritus in Alagille Syndrome? Have all relevant comparators for maralixibat been included in the scope?** As is already mentioned in the scope, off-label therapies include rifampicin, bile salt-binding agents (cholestyramine), opioid antagonists, and selective serotonin re-uptake inhibitors (SSRI) (Ayoub and Kamath, 2020). All relevant comparators for maralixibat have been included in the scope.	

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		Q14. Are the outcomes listed appropriate? Are there other outcomes that should be listed? *See outcomes section above.* **Q15. Are there any subgroups of people in whom maralixibat is expected to be more clinically effective and cost effective or other groups that should be examined separately?** No. **Q16. Do you consider that the use of maralixibat can result in any potential substantial health-related benefits that are unlikely to be included in the QALY calculation?** **Please identify the nature of the data which you understand to be available to enable the committee to take account of these benefits**. Indirect effects include reduction in productivity, levels or work and financial stability, as well as quality of sleep for carers (Quadrado et al., 2022). In addition to this, higher levels of anxiety and depression were seen in carers compared to the general population (Quadrado et al., 2022). Indirect effects, that do not currently have published evidence available, include reduction in educational engagement attainment. Patients or siblings of patients may miss days of school and will not fulfil societal goals of achieving higher education and contributing to the economy. Health-related benefits of maralixibat in alleviating the trauma of paediatric surgery, for both patient and carer, are not likely to be captured within the	

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		QALY calculation. Post-traumatic stress is going to be higher in patients and carers with ALGS post-surgery than those of the general population (Turgoose et al., 2021). In addition to the above, the role of caregiver will typically be informal for chronic diseases, and the majority of informal caregivers are women (Navaie-Waliser et al., 2002; Toledano-Toledano and Luna, 2020). As a group, these women provide physical, psychological and emotional support, that contributes to their own burden and further contributes to inequality in burden experienced by women caregivers, compared with caregivers of all genders. This will not be captured in the QALY calculation. • **Q17. NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that the proposed remit and scope may need changing in order to meet these aims. In particular, please tell us if the proposed remit and scope:** • **could exclude from full consideration any people protected by the equality legislation who fall within the patient population for which maralixibat is licensed;** • **could lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population, e.g. by making it more difficult in practice for a specific group to access the technology;**	

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		• **could have any adverse impact on people with a particular disability or disabilities.** • **Please tell us what evidence should be obtained to enable the committee to identify and consider such impacts.** Nothing to note.	
Additional comments on the draft scope	Genetic Alliance UK	No comments.	
	Children's Liver Disease Foundation	No comments.	
	Mirum Pharmaceuticals	None. References: Ayoub, M.D., Kamath, B.M., 2020. Alagille Syndrome: Diagnostic Challenges and Advances in Management. Diagnostics (Basel) 10, 907. https://doi.org/10.3390/diagnostics10110907 Cuenca, A., Yeh, H., 2019. Improving Patient Outcomes Following Pediatric Liver Transplant: Current Perspectives. Transplant Research and Risk Management Volume 11, 69–78. https://doi.org/10.2147/TRRM.S183382 Diaz-Frias, J., Kondamudi, N.P., 2021. Alagille Syndrome, in: StatPearls. StatPearls Publishing, Treasure Island (FL). Elisofon, S.A., Emerick, K.M., Sinacore, J.M., Alonso, E.M., 2010. Health status of patients with Alagille syndrome. J Pediatr Gastroenterol Nutr 51, 759–765. https://doi.org/10.1097/MPG.0b013e3181ef3771 Hansen, BE, Kamath, BM, Vandriel, SM, Vig, P, Garner, W, 2021. Application of real-world evidence analytics: A 6-year event-free survival analysis in	

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		Turgoose, D.P., Kerr, S., Coppi, P.D., Blackburn, S., Wilkinson, S., Rooney, N., Martin, R., Gray, S., Hudson, L.D., 2021. Prevalence of traumatic psychological stress reactions in children and parents following paediatric surgery: a systematic review and meta-analysis. BMJ Paediatrics Open 5, e001147. https://doi.org/10.1136/bmjpo-2021-001147 Vandriel et al., 2020. GALA EASL 2020. Vandriel, S.M., Li, L., She, H., Wang, J., Gilbert, M.A., Hansen, B.E., Kamath, B.M., et al., 2023. Natural history of liver disease in a large international cohort of children with Alagille syndrome: Results from the GALA study. Hepatology 77, 512–529. https://doi.org/10.1002/hep.32761	

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

British Liver Trust

Metabolic Support UK