Highly Specialised Technologies (HST) criteria checklist

Maralixibat for treating cholestatic disease in Alagille Syndrome [ID3941]

### Introduction

The NICE HST criteria checklist is to highlight where a technology meets/partially meets or does not meet the criteria for routing to the HST programme. Its purpose is to show the details of why a technology may not be appropriate for HST evaluation, but also where it has been identified as suitable. For more information, please see [section 7 of NICE health technology evaluation topic selection: the manual](https://www.nice.org.uk/process/pmg37/chapter/highly-specialised-technologies)

### Key – does the technology meet the criteria? Please use the colour key to advise if the technology meets the criteria

|  |  |
| --- | --- |
| Met | There is clear and strong evidence that this criterion is met |
| Not met | There is no evidence, limited evidence, or uncertainty that the criterion is met. |

**Expected MA wording: Treatment of cholestatic disease in patients with Alagille Syndrome aged 1 year and older**

| **Number** | **Criterion** | **Description of how the technology meets the criteria** | **Does the technology meet the criteria?** |
| --- | --- | --- | --- |
|  | The condition is very rare defined by 1:50,000 in England | **Live birth/incidence estimate:**   * Incidence at birth (birth prevalence) is estimated between 1 in 30,000 and 1 in 70,000 live births1, 2, 3. * Leonard 2014 et al 1 . estimates that the incidence is 1 in 30,000 to 1 in 50,000 live births * Company stated that the \*\*\*\*\*\*\*\*\*\*\*\*\* estimate includes people with ALGs who do not present with cholestasis. Based on this and clinical opinion, the company concluded that \*\*\*\*\*\*\*\*\*\*\*\*\* estimate is the most plausible for live birth incidence. * However, a recently published review4 reported that: “*1 in 70,000 live births estimate based on the presence of neonatal cholestasis in the pre-molecular diagnostics era. However, following the discovery that mutations in JAGGED1 (JAG1) are responsible for ALGS, through screening of relatives of ALGS mutation positive probands (of which 47% did not meet clinical criteria), the true incidence is likely 1 in 30,000 live births.”*   The technical team therefore considers that the \*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\* incidence estimate chosen by the company might be reasonable, but there is uncertainty and the prevalence estimate should be calculated and considered using both \*\*\*\*\*\*\*\*\*\*\*\*\* and 1 in 30,000 live birth incidence estimates.  **Prevalence estimate:**   * Estimates of prevalence vary between 1 in 30,000 and 1 in 100,000.5 This leads to a prevalence of 565 to 1,885 in England ([using 2020 mid-year England population estimate](https://www.ons.gov.uk/peoplepopulationandcommunity/populationandmigration/populationestimates#timeseries), 56,550,000).6 | Not met |
|  | Normally no more than 300 people in England are eligible for the technology in its licensed indication and no more than 500 across all its indications | **Live birth incidence:**   * there were 610,505 live births in England in 20197, so the incidence equates to about 20 (610,505/30,000) live births each year in England using 1:30,000 estimate. * If using the company’s preferred live birth incidence estimate of \*\*\*\*\*\*\*\*\*\*\*\*\*, the incidence would equate to about \*\*\*\*\*\*\*\*\*\*\*\*\*.   **Population eligible for treatment:**  The company provided a new estimate of \*\*\* patients would be eligible for treatment during the challenge, for this, it:   * chose the \*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\* reported in the literature for live birth incidence for ALGs (ranged between 1 in 30,000 and 1 in 70,000). This translates into about \*\*\*\*\* cases each year; * excluded patients with mild ALGs (\*\*\*\*\*\*\*\*\*\*\*\*). * cited GALA study8, an international dataset for ALGs, which reported that about 59% of ALGs patients with neonatal cholestasis would have had a liver transplant by age 18, therefore won’t be eligible for treatment and leaving 41% of patients eligible.   *However,*   * As mentioned above, for live birth incidence: the NICE technical team considers that \*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\* chosen by the company may be reasonable, but the estimate for eligible population should be calculated and considered using both 1 in \*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\* and 1 in 30,000 (20 cases a year) estimates. * Mild ALGs should be included as it is covered by the company’s expected MA wording; * For the proportion of patients who would have a liver transplant by age 18 and therefore won’t be eligible for maralixibat: * This company’s estimate from GALA study was based on ALGs with neonatal cholestasis, more severe and more likely to have a liver transplant compared with ALGs with non-neonatal cholestasis according to the evidence 9 * Company’s intended MA wording covers ALGs with both neonatal and non-neonatal cholestasis; * A recent systematic review10 reported that between 15% and 47% of ALGs patients underwent liver transplant. * The technical team therefore chose 31%, the median of 15% and 47%, for calculation, instead of the company’s 59% based on GALA study alone. * Based on these consideration, the NICE technical team’s estimate is about \*\*\* patients eligible if using \*\*\*\*\*\*\*\*\*\*\* live birth incidence, and about 915 if using the 1: 30, 000 live birth incidence.   Further, clinicians at the scoping workshop indicated that the incidence and prevalence reported in the literature may be underestimated because Alagille syndrome may be undiagnosed or misdiagnosed due to the varying clinical presentation.11 Experts at the workshop estimated that the incidence and prevalence could be around 10% higher. They also noted that all patients over and under 18 with cholestasis would be eligible for treatment and that treatment is expected to be lifelong. | Not met |
|  | The very rare condition significantly shortens life or severely impairs its quality | Likely met for all patients that would receive treatment, although the clinical presentation of Alagille syndrome is very variable.  People who are diagnosed in infancy are often diagnosed because of liver disease causing symptoms from the first few months of life.  Liver disease in Alagille syndrome, if present, may range in severity from jaundice or mild cholestasis to severe, progressive liver disease that can potentially result in liver failure.11  At the scoping workshop, clinical and patient experts explained that the pruritus associated with cholestasis in Alagille syndrome severely impairs the quality of life, impacting on all aspects of the child’s life, including sleep, appetite, education, relationships, and ability to take part in everyday activities. This has an impact on the caregivers and the wider family.  The disease can stabilise and symptoms may improve, but evidence from GALA study suggested that almost 60% of ALGs patients with neonatal cholestasis will have a liver transplant before 18 years of age.11 Currently there is no way to predict whether liver symptoms in infancy will resolve or progress.12  It was reported that 20-year life expectancy of patients with Alagille syndrome was 75%. The 20-year life expectancy was higher (80%) for patients who did not require a liver transplant, and lower (60%) for patients who did require a liver transplant.13 | Met |
|  | There are no other satisfactory treatment options, or the technology is likely to offer significant additional benefit over existing treatment options. | Current treatment for Alagille Syndrome focuses on alleviating symptoms. Treatments to reduce itching may include ursodeoxycholic acid, cholestyramine, rifampicin, naltrexone, ondansetron, SSRIs and antihistamines such as chlorphenamine.12, 14,15 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.12  If Alagille Syndrome does not respond to drug and dietary therapies, a partial biliary diversion may be carried out,14 although this is rare in the UK. At the scoping workshop, clinical experts explained that liver transplant is the only treatment for the underlying liver failure. | Met |

**References**

1 Leonard, L.D. *et al.* (2014) ‘Clinical utility gene card for: Alagille Syndrome (ALGS)’, *European Journal of Human Genetics*, 22(3).

2 Kamath, B. *et al.* (2003) ‘Consequences of JAG1 mutations’, *Journal of Medical Genetics*, 40(12), pp. 891–895. doi:10.1136/jmg.40.12.891.

3 MedLine Genetics (2021) *Alagille syndrome: MedlinePlus Genetics*. Available at: <https://medlineplus.gov/genetics/condition/alagille-syndrome> (Accessed December 2021)

4 [Ayoub and Kamath 2020](https://www.mdpi.com/2075-4418/10/11/907/htm)  Review: Alagille Syndrome: Diagnostic Challenges and Advances in Management; Access online September 2022

5. Diaz-Frias J, Kondamudi NP. Alagille Syndrome. [Updated 2021 Jun 26]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2021 Jan-. Available at: <https://www.ncbi.nlm.nih.gov/books/NBK507827>.

6 Office for National Statistics (2021) Estimates of the population for the UK, England and Wales, Scotland and Northern Ireland. Available at <https://www.ons.gov.uk/peoplepopulationandcommunity/populationandmigration/populationestimates/datasets/populationestimatesforukenglandandwalesscotlandandnorthernireland> Accessed December 2021.

7 Office for National Statistics (2020) Births in England and Wales: summary tables. Available at [https://www.ons.gov.uk/peoplepopulationandcommunity/birthsdeathsandmarriages/livebirths/datasets/birthsummarytables. Accessed September 2021](https://www.ons.gov.uk/peoplepopulationandcommunity/birthsdeathsandmarriages/livebirths/datasets/birthsummarytables.%20Accessed%20September%202021).

8 GALA study: <https://www.galastudy.com/> Access online September 2022

9 Lykavieris et al. 2001. [Outcome of Liver Disease in Children with Alagille Syndrome: A Study of 163 Patients](https://journals.lww.com/jpgn/Fulltext/2002/07000/Outcome_of_Liver_Disease_in_Children_with_Alagille.25.aspx)**.** Access online September 2022

# **10** Kamath et al. 2018**.** [Systematic Review: The Epidemiology, Natural History, and Burden of Alagille Syndrome](https://journals.lww.com/jpgn/Fulltext/2018/08000/Systematic_Review__The_Epidemiology,_Natural.3.aspx). Accessed online September 2022

11 Vandriel, S, Liting, L et al. (2020). Clinical Features and Natural History of 1154 Alagille Syndrome Patients: Results from the International Multicenter GALA Study Group.

12 Genetic and Rare Diseases Information Center. Alagille Syndrome. Available at [https://rarediseases.info.nih.gov/diseases/804/alagille-syndrome. Accessed September 2021](https://rarediseases.info.nih.gov/diseases/804/alagille-syndrome.%20Accessed%20September%202021).

13 Emerick KM, Rand EB, Goldmuntz E, Krantz ID, Spinner NB, Piccoli DA. [Features of Alagille syndrome in 92 patients: frequency and relation to prognosis](https://aasldpubs.onlinelibrary.wiley.com/doi/abs/10.1002/hep.510290331). Hepatology. 1999;29(3):822-829. doi:10.1002/hep.510290331

14 Children’s Liver Disease Foundation. Alagille Syndrome. Available at https://childliverdisease.org/liver-information/childhood-liver-conditions/alagille-syndrome/ Accessed September 2021.

15 National Organization for Rare Disorders. Alagille Syndrome. Available at <https://rarediseases.org/rare-diseases/alagille-syndrome/>. Accessed September 2021.