New Drug Fact Blast

Clinical Services

Drug/Manufacturer:	**Bylvay™ (odevixibat) [Albireo Pharma, Inc.]**
Dosage Formulations:	Oral pellets: 200 mcg, 600 mcg Capsules: 400 mcg, 1200 mcg
FDA Approval Date: **FDB File Date:**	FDA: July 20, 2021 FDB: August 1, 2021
Indication:	The treatment of pruritis in patients 3 months of age and older with progressive familial intrahepatic cholestasis (PFIC). Limitation of use: may not be effective in PFIC Type 2 patients with *ABCB11* variants resulting in non-functional or complete absence of bile salt export pump protein (BSEP-3).
Mechanism of Action:	Bylvay is a reversible inhibitor of the ileal bile acid transporter (IBAT) that decreases the reabsorption of bile acids (primarily the salt forms) from the terminal ileum. The complete mechanism by which Bylvay improves pruritis in PFIC is unknown.
Dose/ Administration:	• Bylvay is to be initiated at a dose of 40 mcg/kg once daily in the morning with a meal. • If no improvement in pruritis after 3 months, may increase dosage in 40 mcg/kg increments up to 120 mcg/kg once daily not to exceed a total daily dose of 6 mg.

	Recommended Dosage of Bylvay for 40 mcg/kg/day*	
Body Weight (kg)	**Total Daily Dose (mcg)**	**Number of Capsules or Oral Pellets**
≤ 7.4	200	1 (200 mcg oral pellet)
7.5 – 2.4	400	2 (200 mcg oral pellets)
12.5 – 17.4	600	3 (200 mcg oral pellets)
17.5 – 19.4	800	4 (200 mcg oral pellets)
19.5 – 25.4	800	2 (400 mcg capsules)
25.5 – 35.4	1200	1 (1200 mcg capsule)
35.5 – 45.4	1600	4 (400 mcg capsules)
45.5 – 55.4	2000	5 (400 mcg capsules)
≥ 55.5	2400	2 (1200 mcg capsules)

**FDA-approved prescribing information does not include the 600 mcg oral pellets here.*

- Oral pellets: Intended for use in patients weighing less than 19.5 kg. Contents of the shell containing the oral pellets are to be mixed with up to 2 tablespoons of soft food (apple sauce, oatmeal, banana/carrot puree, chocolate/rice pudding). The shell containing the oral pellets should not be swallowed whole.
- Capsules: Intended for use in patients weighing 19.5 kg or greater. Capsules are to be swallowed whole with a glass of water and cannot be crushed or chewed. They may also be opened, sprinkled, and mixed with a small amount of soft food.
- Both the oral pellets and capsules should be stored at room temperature. The entire dose is to be consumed immediately; mixture cannot be stored for future use. Each dose should be followed with water.

- Individuals exclusively requiring the intake of liquid foods should not use Bylvay as the product is not to be mixed with liquids.

Disease State Clinical Highlights:

- Progressive familial intrahepatic cholestasis (PFIC), first described in the mid-1900s, is a group of rare autosomal recessive liver disorders characterized by mutations in genes encoding proteins involved in the hepatocellular transport system. The genetic mutations lead to a disruption in bile formation. Under normal conditions, bile acids are produced in the liver utilizing cholesterol and are stored in the gallbladder. Bile acids are released into the small intestine in response to food and are essential for digestion and the absorption of dietary fats and fat-soluble vitamins (vitamins A, D, E, and K). Post-digestion, bile acids are reclaimed in the distal part of the small intestine, the terminal ileum, by the IBAT. IBAT initiates the transport of bile acids back through the portal vein and into the liver via enterohepatic circulation. Defects along this pathway can result in the build-up of toxic bile acids, leading to hepatocyte damage, inflammation, and liver injury.
- The hallmark sign of PFIC, cholestasis, is associated with jaundice, malabsorption, and intense pruritis. Patients can also present with splenomegaly, hepatomegaly, and impaired growth.
- The pruritis associated with PFIC is often described as the most bothersome symptom and may lead to bleeding, excoriations, scars, and discomfort that impacts activities of daily living and sleep. The exact mechanism by which pruritis occurs is unknown but it is proposed that the itching is induced via the stimulation of nonmyelinated subepidermal free nerve ends resulting from increased serum bile acids.
- PFIC typically develops in infancy; median age of symptom onset is 2 months with 78% of patients developing jaundice but it can also develop into young adulthood.
- There are an estimated 600 cases of PFIC in the United States and 15,000 worldwide. Incidence is estimated at 1 in 50,000 to 1 in 100,000 births.
- Disease progression can occur rapidly with resultant fibrosis and end-stage liver disease occurring before adulthood. Additional complications include portal hypertension, cirrhosis, and hepatocellular carcinoma. If left untreated, PFIC is fatal.
- Diagnosis is established by an evaluation of patient history, physical examination, radiologic or histological evaluations, liver function tests (e.g., gamma-glutamyltransferase [GGT], aspartate aminotransferase [AST], alanine transaminase [ALT]), bile acid tests, liver biopsy, and genetic testing.

<u>Subtypes</u>

- The three main subtypes of PFIC are Types 1, 2, and 3. The most severe forms, Types 1 and 2, are caused by a depletion of bile acid secretion. Type 3, the rarest form, is the result of impaired bile phospholipid secretion. Although the affected gene differs between subtypes, all are caused by defects in the genes that encode proteins associated with the hepatocellular transport system.

	PFIC 1	PFIC 2	PFIC 3
Protein Deficiency	FIC1	BSEP	MDR3
Mutated Gene	*ATP8B1*	*ABCB11*	*ABCB4*
Clinical Presentation	• Intense pruritis • Extrahepatic symptoms • Diarrhea • Variable: cough, pancreatitis, hearing loss, wheezing, stunted growth • Normal GGT cholestasis	• Intense pruritis • Potential to develop hepatocellular carcinoma and cholangiocarcinoma • Gallstones • Normal GGT cholestasis	• Mild-moderate pruritis • Reduced bone density • Potential to develop hepatocellular carcinoma and cholangiocarcinoma • Gallstones • Elevated GGT cholestasis

Clinical Outcomes/ Management	• Moderate progression • May progress to cirrhosis and end-stage liver disease, most often in second or third decade of life • Can develop posttransplant hepatic steatosis and diarrhea • Extrahepatic symptoms may develop or worsen post-transplant	• Moderate to rapid progression • Biliary diversion surgery success can be dependent on the genetic defect • Liver transplant may lead to antibody induced BSEP deficiency, which may lead to disease recurrence	• Extremely variable progression • Patients with MDR3 expression have better responses to ursodiol • Biliary diversion may not work as well compared to other subtypes • Liver transplant is curative

Laboratory Findings in PFIC subtypes (N=normal, H=high/elevated, L=low/depleted)			
	PFIC Type 1	**PFIC Type 2**	**PFIC Type 3**
Serum GGT	N	N	H
Serum direct bilirubin	H	H	H
Serum bile acids	H (++)	H (+++)	H (+)
Serum ALP	H	H	H
Serum ALT	H	H	H
Biliary phospholipids	N	N	L
Serum5'nucelotidase	H	H	H
Serum AFP	N	H	N

AFP: alphafetoprotein, ALP: alkaline phosphatase; ALT: alanine aminotransferase; GGT: gamma glutamyl transferase, PFIC: progressive familial intrahepatic cholestasis

Drug Clinical Highlights:

- Bylvay, a non-systemic ileal bile acid transport inhibitor acting locally in the small intestine, is the first and only FDA-approved medication for the treatment of pruritis associated with PFIC.
- The FDA granted Bylvay Fast Track Review, Rare Pediatric Disease and Orphan Drug designations.

Warnings/Precautions:

- Liver test abnormalities
  - Prior to initiating Bylvay, the baseline pattern of variability of liver tests (e.g., ALT, AST, total bilirubin, direct bilirubin [DB], International Normalized Ratio [INR]) should be documented. Monitoring should continue during treatment and therapy should be interrupted if new onset liver test abnormalities occur or symptoms consistent with clinical hepatitis are observed.
  - Treatment may be reinitiated at the lowest dose 40 mcg/kg and increased as tolerated once liver test abnormalities return to baseline and/or stabilize at a new baseline value. If abnormalities recur, permanent discontinuation of therapy should be considered.
  - Permanent discontinuation is necessary upon the occurrence of a hepatic decompensation event such as variceal hemorrhage, ascites, or hepatic encephalopathy.
- Diarrhea
  - If diarrhea occurs, monitor for dehydration and treat promptly.
  - Treatment may be interrupted for cases of persistent diarrhea and restarted at a dose of 40 mcg/kg and increased as clinically appropriate once symptoms resolve.
  - If diarrhea persists and no alternate etiology is identified, stop Bylvay.
- Fat-soluble vitamin deficiency (vitamins A, D, E, and K)
  - Fat-soluble vitamin deficiencies may be present at baseline in patients with PFIC and Bylvay may further affect fat-soluble vitamin absorption. Obtain baseline serum fat-soluble vitamin levels and monitor during treatment, along with any clinical manifestations.

- If fat-soluble vitamin deficiency is diagnosed, provide supplementation.
- Discontinue treatment with Bylvay if deficiency persists or worsens despite adequate supplementation.

Contraindications: none

Drug Interactions: bile acid binding resins (e.g., cholestyramine, colesevelam, colestipol) should be administered at least 4 hours before or after Bylvay. Bile acid binding resins can bind to Bylvay in the gastrointestinal tract, which may reduce Bylvay efficacy.

Pregnancy/Lactation:

- Based on findings from animal reproduction studies, Bylvay may cause cardiac malformations when a fetus is exposed during pregnancy. In pregnant rabbits treated orally with Bylvay during organogenesis, an increased incidence of malformations in fetal heart, great blood vessels, and other vascular sites occurred at all doses. Bylvay was shown to cross the placenta in pregnant rats.
- Bylvay has low absorption following oral administration, and breastfeeding is not expected to result in exposure of the infant to Bylvay at the recommended doses. Treatment with Bylvay may reduce absorption of fat-soluble vitamins; levels should be monitored, and intake of fat-soluble vitamins increased if deficiency is observed during lactation. The development and health benefits of breastfeeding should be considered along with the mother's clinical need for Bylvay and any potential adverse effects on the breastfed child from Bylvay or from the underlying maternal condition.

Hepatic impairment: Patients with PFIC may have impaired hepatic function at baseline. The efficacy and safety in PFIC patients with clinically significant portal hypertension and in patients with decompensated cirrhosis have not been established.

Clinical Studies

- PEDFIC 1 (n=62) (NCT03566238): randomized, double-blind, placebo-controlled, Phase III, 24 week efficacy and safety study. Patients were randomized to placebo (n=20), Bylvay 40 mcg/kg (n=23), or Bylvay 120 mcg/kg (n=19) once daily.
  - Key Inclusion Criteria:
    - Clinical diagnosis of PFIC Type 1 or 2 and body weight above 5 kg
    - Genetic confirmation of PFIC 1 or PFIC 2
    - History of significant pruritis (average scratching score ≥ 2 [medium scratching])
  - Key Exclusion Criteria:
    - Pathologic variations of the *ABCB11* gene that predict complete absence of the BSEP protein
    - INR > 1.4
    - ALT or total bilirubin > 10 times upper limit of normal
    - Past medical history or ongoing presence of other types of liver disease (e.g., biliary atresia, benign recurrent intrahepatic cholestasis)
    - Biliary diversion surgery within 6 months prior to start of screening period
    - Liver transplant or planned liver transplant within 6 months of randomization
    - Decompensated liver disease
  - Key Baseline Characteristics
    - Patients enrolled were ages 6 months to 17 years of age
    - 50/62 patients were receiving ursodiol
    - 27% of patients had PFIC Type 1 and 73% had Type 2
    - Mean (standard error [SE]) scratching score was 2.9 (0.08)

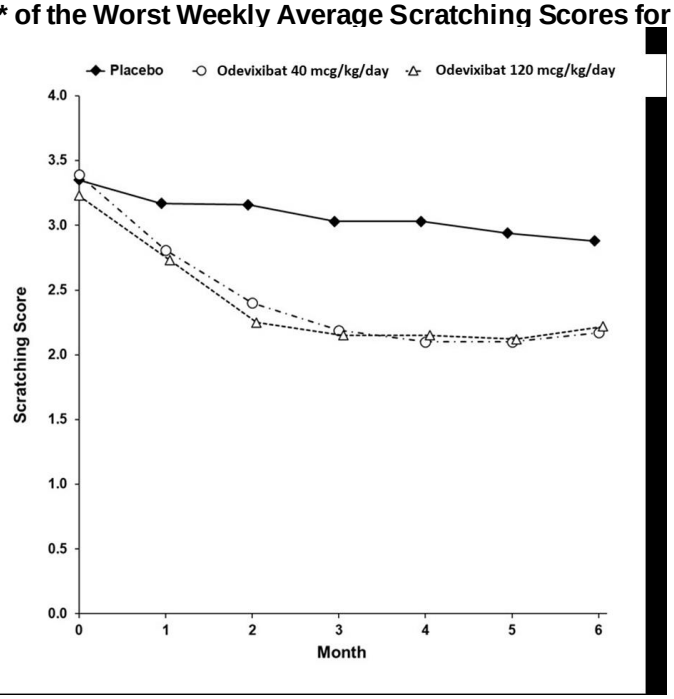
- Baseline median (range) ALT, AST, and total bilirubin were 65 (16-798) U/L, 83.5 (32-405) U/L, and 2.2 (0.2-18.6) mg/dL respectively

- Primary Outcome Measure: proportion of positive pruritis assessments compared to placebo at the subject level over the 24 week treatment period based on the Albireo observer-reported outcome (ObsRO) instrument. A positive pruritis assessment was defined as a scratching score of ≤ 1 or at least a one-point drop from baseline on the Albireo ObsRO instrument. Scratching measured twice daily on a scale of 0 (no scratching) to 4 (worst possible scratching).

	Bylvay 40 mcg/kg/day (n=23)	Bylvay 120 mcg/kg/day (n=19)	Placebo (n=20)
Mean[a] Percentage of Assessments Over the Treatment Period Scored as 0 (no Scratching) or 1 (a little scratching) (%)*			
Mean (SE)	35.4 (8.1)	30.1 (9.0)	13.2 (8.7)
Mean Difference vs. Placebo (95% CI)	22.2 (4.7, 39.6)	16.9 (-2.0, 35.7)	

** Displays the mean of patients' worst weekly average scratching scores in each treatment group for each month, where the weekly average utilized the worst score from each day (morning or evening).*
[a] Based on least squares means from analysis of covariance model with daytime and nighttime baseline pruritis scores as covariates and treatment group and stratification factors (i.e., PFIC type and age category) as fixed effects.

Mean* of the Worst Weekly Average Scratching Scores for Each Month



** Figure presents least squares means*
Based on a mixed model repeated measure (MMRM) analysis accounting for baseline score, treatment group, time (in months), treatment-by-baseline interaction, treatment-by-time interaction, and stratification factors (i.e., PFIC type and age category). Missing data were accounted for using placebo-reference multiple imputation.

- 13 (21%) patients discontinued trial prematurely either due to no improvement in pruritis (n=11) or due to adverse reactions (n=2). 5/20 (25%) discontinued from the placebo arm and 8/42 (19%) discontinued from the Bylvay arms.

- Adverse reactions: (reported in ≥ 2% and at a rate greater than placebo)

	Bylvay 40 mcg/kg/day N=23 n (%)	Bylvay 120 mcg/kg/day N=19 n (%)	Total Bylvay N=42 n (%)	Placebo N=20 n (%)
Any adverse event	19 (82.6)	16 (84.2)	35 (83.3)	17 (85.0)
Diarrhea*	9 (39.1)	4 (21.1)	13 (31.0)	2 (10.0)
ALT/AST increased	3 (13.0)	4 (21.1)	7 (16.7)	1 (5.0)
Vomiting	4 (17.4)	3 (15.8)	7 (16.7)	0
Abdominal pain	3 (13.0)	3 (15.8)	6 (14.3)	0
Blood bilirubin increased	3 (13.0)	2 (10.5)	5 (11.9)	2 (10.0)
Fat-soluble vitamin deficiency	0	3 (15.8)	3 (7.1)	1 (5.0)
Splenomegaly	0	2 (10.5)	2 (4.8)	0
Cholelithiasis	0	1 (5.3)	1 (2.4)	0
Dehydration	0	1 (5.3)	1 (2.4)	0
Fracture	1 (4.3)	0	1 (2.4)	0

**One patient withdrew from the trial due to an adverse event of diarrhea.*

  - Treatment interruption due to diarrhea occurred in 2 patients with 3 events during treatment with Bylvay 120 mcg/kg/day. Treatment interruption ranged from 3 to 7 days. One patient treated with Bylvay 120 mcg/kg/day withdrew from Trial 1 (PEDFIC 1) due to treatment-emergent/persistent diarrhea.

Number of patients with*:	Bylvay 40 mcg/kg (N=20) n (%)	Bylvay 120 mcg/kg (N=19) n (%)	Total Bylvay (N=42) n (%)	Placebo (N=20) N (%)
ALT increase over baseline ≥ 150 U/L	2 (8.7)	2 (10.5)	4 (9.5)	0
AST increase over baseline by ≥ 150 U/L	1 (4.3)	3 (15.8)	4 (9.5)	0
TB increase over baseline by ≥ 2 mg/dL	4 (17.4)	1 (5.3)	5 (11.9)	1 (5.0)
DB increase over baseline by ≥ 1 mg/dL	5 (21.7)	2 (10.5)	7 (16.7)	2 (10.0)

ALT: alanine aminotransferase, AST: aspartate aminotransferase, DB: direct bilirubin, TB: total bilirubin
**Patients enrolled in the clinical trial had abnormal liver tests at baseline*

  - Treatment-emergent elevations of liver tests or worsening of liver tests relative to baseline values were observed. Treatment interruption days ranged from 3 to 124 days.

- PEDFIC 2 (n=79) (NCT03659916): open-label, single-arm, Phase III, 72 week long-term extension safety and efficacy study in patients with PFIC Types 1, 2, or 3.
  - Included patients aged 4 months to 25 years of age with average weight of 18 kg
  - Cohort 1: 56 patients from PEDFIC 1 (including 11 of the 13 that discontinued therapy); Cohort 2: 23 additional patients who did not participate in PEDFIC 1.
  - Patients received Bylvay 120 mcg/kg once daily
  - 12 patients discontinued Bylvay, two of which underwent surgery (1 had a liver transplant, 1 biliary diversion surgery) due to pruritis that was unresponsive to Bylvay
  - Only interim analysis is currently available, but the manufacturer has reported similar adverse events as seen in PEDFIC 1 in addition to improvements in serum bile acid reduction, pruritis, growth, and sleep.

- Although not represented in the FDA-approved prescribing information, manufacturer-derived articles indicate that Bylvay achieved a statistically significant improvement in pruritis assessment (p=0.004) and reduction in serum bile acid response (p=0.003) utilizing 96 weeks of collective data from PEDFIC 1 and PEDFIC 2. Improvements in each endpoint compared to placebo were observed as early as 4 weeks. Therapy with Bylvay has been described as well-tolerated with very low incidence of

diarrhea/frequent bowel movements (9.5% of treated patients vs. 5.0% of placebo patients) using data from PEDFIC 1, per the manufacturer.

<u>European Approval</u>

- PEDFIC 1 was used to garner Bylvay approval by the European Commission (EC) for the treatment of progressive familial intrahepatic cholestasis (PFIC) in patients aged 6 months or older.
- The primary outcome identified in PEDFIC 1 for Europe and the rest of the world was bile acid reduction compared to placebo (secondary outcome measure for US data). Bile acid reduction was defined as bile acid reduction ≥ 70% or reaching a bile acid level ≤ 70 µmol/L. Change in pruritis was a secondary endpoint for the European data.
- Although the positive results were maintained in the long-term open label trial, the European Medicines Agency's (EMA) Committee for Medicinal Products for Human Use (CHMP) has requested a registry-based efficacy follow-up study to confirm if Bylvay delays disease progression and the requirement for liver transplantation. Final report submission date: 12/2027.

- Bylvay is Albireo's first commercially available drug in the United States. It will be available through select specialty pharmacies Accredo, Optum Frontier, and PANTHERRx Rare.

Price Per Unit (WAC):

- 200 mcg oral pellets: $220/oral pellet; $6,600/30 days
- 400 mcg capsule: $440/capsule; $13,200/30 days
- 600 mcg oral pellet: $660/oral pellet; $19,800/30 days
- 1,200 mcg oral capsule: $1,320/capsule; $39,600/30 days
- Example Bylvay cost based on 18 kg patient (pellets are intended for weight < 19.5 kg):

	40 mcg/kg Dose	80 mcg/kg Dose	120 mcg/kg Dose
Calculated Daily Dose	720 mcg	1,440 mcg	2,160 mcg
Product Utilized*	1-200 mcg oral pellet plus 1-600 mcg oral pellet	2-200 mcg oral pellet plus 2-600 mcg oral pellets	4-600 mcg oral pellets
Cost/Dose	$880	$1,760	$2,640
Cost/Year	$321,200	$642,400	$963,600

**If calculated daily dose fell between two available dosage strengths, the dose was rounded up to the nearest dosage strength to correlate with the guidance presented in the prescribing information.*

- Albireo states that Bylvay is priced at parity to other medications used to treat rare diseases and its price is based on the rarity of PFIC, the few effective alternative treatments, and Bylvay's potential to delay or prevent liver damage and liver transplant. The manufacturer has estimated an annual price of $385,000.

Therapeutic Alternatives:

- Pharmacological PFIC Treatment Options
  - Goals of therapy: relieve pruritis, improve nutritional status, slow disease progression, and prevent complications of advanced liver disease.
  - For all PFIC patients, drug therapy is the first line of treatment. Agents such as ursodeoxycholic acid (UDCA/Ursodiol), cholestyramine, rifampin, and antihistamines may be utilized for pruritis management; however, often prove ineffective. Additional components of the drug regimen may include opiate antagonists, ondansetron, corticosteroids, propofol, and carbamazepine.
  - Dietary fat as medium chain triglycerides which do not require bile salts for absorption, as well as supplementation with fat-soluble vitamins (A, D, E, and K), increased calcium intake (800-2,000 mg/day), and adequate sunlight exposure. Water-soluble vitamins are administered at 1-2 times the recommended daily allowance.

	Ursodiol	Cholestyramine	Rifampin
Mechanism of Action	Non-toxic hydrophilic bile acid that reverses potential hepatotoxicity of accumulating endogenous bile acids. Regulates bile acid distribution and reduces amount of cholesterol in bile.	Bile acid binding resin that induces liver enzyme activity and increases bilirubin excretion.	Upregulates detoxification enzymes and export pumps through farnesoid X-receptor (FXR) dependent mechanisms. Indirectly induces hydroxylation of bile salts which are further glucuronidated and excreted in urine. Induces excretion of bilirubin.
Dose	10-30 mg/kg orally once daily	4 - 8g/day orally 1 hour before or 4-6 hours after meals	5-10 mg/kg/day
Notes	• Initial treatment for all PFIC subtypes • Ineffective in roughly one-third of Type 3 patients with total defect in MDR3 gene expression • Commonly used as the standard of care due to potential to relieve pruritis and prevent liver damage	• Has not been found to be useful in PFIC Types 1 or 2	• Off-label • Risk of hepatotoxicity • Multiple drug interactions
Estimated Annual Cost*	• $1,066	• $871	• $292

**Based on 18 kg patient utilizing high end of therapeutic dose range*

- Despite the optimal use of pharmacological therapies, disease progression often necessitates biliary diversion surgery or liver transplant by the age of 30. Success rates of diversion procedures are highest when performed during the early stages of the disease.

- Non-Pharmacological PFIC Treatment Options
  - Nasobiliary drainage
    - Non-surgical, temporary option in which a nasobiliary drain is endoscopically inserted into and drains the bile ducts. Patient's response may predict future response to biliary diversion.
  - Partial external biliary diversion (PEBD)
    - Surgical procedure in which a jejunal conduit is created between the fundus of the gallbladder and abdominal skin. A permanent stoma is created which allows bile acids to drain externally into an ostomy. PEBD is performed to a high degree in Type 1 and 2 patients and may postpone or prevent the need for liver transplantation.
  - Partial internal biliary diversion and ileal exclusion/bypass
    - Surgical procedures that do not require an external ostomy but data supporting their use is limited. Symptom recurrence by the end of year one is common with ileal exclusion due to ileal adaptation.
  - Liver transplant
    - PFIC represents one of the five most common indications for liver transplantation in children, accounting for 10-15% of cases.
    - Reserved for severe cases in which patients have advanced cirrhosis, liver failure, or liver cancer, or are unresponsive to other interventions.
    - May worsen or fail to improve extrahepatic manifestations, such as diarrhea, liver steatosis, and short stature, particularly in patients with PFIC Type 1, a multiorgan disease.

	▪ Post-transplantation recurrence has been observed in up to 8% of patients with Type 2 due to antibodies against BSEP.
Prior Authorization Approval Criteria:	**Must meet the following criteria:** Initial Therapy: • Participant has documented baseline liver tests (ALT, AST, TB, DB, INR) **AND** • Prescribed by or in consultation with hepatologist, gastroenterologist or other specialists in the treated disease state **AND** • Age ≥ 3 months **AND** • Genetic testing confirms pathogenic variant indicating presence and type of PFIC **AND** • Genetic testing does not indicate PFIC Type 2 with *ABCB11* variants encoding for nonfunction or absence of BSEP-3 **AND** • Presence of moderate to severe pruritis as evidenced by clinically accepted scales/tools (e.g., Whittington scale) **AND** • Participant lacks lifetime history of liver transplant or decompensated cirrhosis **AND** • Participant history demonstrates therapeutic trial of ursodiol (defined as 60/90 days) **AND** • Participant (female of childbearing age) is not pregnant **AND** • Dose does not exceed 6 mg/day **AND** • Initial approval period: 6 months Continuation of Therapy: • Participant demonstrates compliance to therapeutic regimen (defined as 90/120 days) • Documentation of benefit of therapy as evidenced by a reduction in pruritic symptoms **Additional Provider Diagnostic/Monitoring Criteria, if desired:** • Monitor liver tests during treatment (ALT, AST, TB, DB, INR). If abnormalities occur, consider dose reductions or treatment interruption. Persistent/recurring abnormalities should prompt a consideration to discontinue therapy. • Monitor for dehydration. Interrupt therapy if diarrhea is persistent and discontinue if it persists after retreatment. • Monitor for fat-soluble vitamin deficiency at baseline as well as during treatment and supplement as necessary. Discontinue if deficiencies persist despite appropriate supplementation. • Monitor bile acid level at baseline and during treatment. • Participant (female of appropriate age) is utilizing concurrent birth control methods.

Implication to State Medicaid Program:	• LOE: 2034
	• Albireo "believes that its cash and cash equivalents will fund its operating expenses and capital expenditure requirements into 2023, which should be sufficient to launch Bylvay and expansion beyond PFIC."
	• Bylvay is in Phase 3 trials with Orphan Designations for two other rare pediatric cholestatic liver diseases:
	  ○ Alagille syndrome: ASSERT trial (NCT04674761). Results expected 2022.
	  ○ Biliary atresia: BOLD trial (NCT04336722). Results expected 2024.
	• Livmarli™ (maralixibat), manufactured by Mirum Pharmaceuticals, was approved by the FDA on September 29, 2021 for the treatment of pruritis in patients with Alagille syndrome.
	  ○ Livmarli has the same mechanism of action as Bylvay and is currently in Phase III trials for PFIC and biliary atresia.
	  ○ ICONIC study (n=31) (NCT02160782): 48-week, Phase 2 study that included children with Alagille syndrome with up to 6 years of follow-up. Patients showed significant reductions in both bile acid levels and pruritis.

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