CADTH REIMBURSEMENT REVIEW

Patient and Clinician Group Input

Odevixibat (Bylvay)

(Medison Pharma Canada Inc.)

Indication: Odevixibat is indicated for the treatment of cholestatic pruritus in patients with Alagille syndrome (ALGS).

March 18, 2025

This document compiles the input submitted by patient groups and clinician groups for the file under review. The information is used by CADTH in all phases of the review, including the appraisal of evidence and interpretation of the results. The input submitted for each review is also included in the briefing materials that are sent to expert committee members prior to committee meetings.

Disclaimer: The views expressed in this submission are those of the submitting organization or individual. As such, they are independent of CADTH and do not necessarily represent or reflect the views of CADTH. No endorsement by CADTH is intended or should be inferred.

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Patient Input Template for CADTH Reimbursement Reviews

Name of Drug: Bylvay
Indication: Odevixibat is indicated for the treatment of cholestatic pruritus in patients with Alagille syndrome (ALGS)
Name of Patient Group: Alagille Syndrome Alliance
Author of Submission: Roberta Smith, President, and Cher Bork, Executive Director

1. About Your Patient Group

The **Alagille Syndrome Alliance (ALGSA)** is a 501(c)(3) global patient advocacy organization dedicated to supporting individuals and families affected by Alagille Syndrome (ALGS). Our mission is *"Mobilizing resources, facilitating connections, promoting unity, and advocating for a cure to inspire, empower, and enrich the lives of people affected by Alagille Syndrome."*

Since our founding in 1993, the ALGSA has become the leading organization focused solely on Alagille Syndrome. We support the global ALGS community through a wide range of programs and services, including our international family conference, financial assistance programs, disease education resources, and family support initiatives.

The ALGSA is deeply committed to advancing scientific research and driving progress toward better treatments and a cure. Our research initiatives include:

- Funding the first three years of the **Global Alagille Alliance (GALA)**
- Creating the **ALGSA Collaborative Scientific Research Grant**
- Establishing the only three-way **Cooperative Research and Development Agreement (CRADA)** with **NIH/NCATS** and **Travere Therapeutics**
- Hosting the biennial **ALGSA Scientific Meeting**
- Managing the ALGS **Patient Registry**
- Launching the **ALGSA Scientific Research Network (ASRN)** in 2024, which focuses on patient-prioritized scientific needs identified through community surveys, polls, patient panels, and one-on-one conversations

The ALGSA collaborates closely with clinicians, researchers, pharmaceutical partners, advocacy organizations, and other stakeholders to improve outcomes and quality of life for those living with Alagille Syndrome.

www.alagille.org

2. Information Gathering

The Alagille Syndrome Alliance (ALGSA) serves as a global leader in patient advocacy and community support for families affected by Alagille Syndrome (ALGS), with a strong presence in Canada and around the world. The ALGSA actively manages or participates in 19 online support pages, including a dedicated Canadian family support page with now 79 participants and two international support pages with now over 3,800 participants—comprised of both caregivers and patients from Canada and globally.

Each year, ALGSA staff engage in over 1,500 direct touchpoints with patients, caregivers, and extended family members—capturing personal stories, treatment experiences, and understanding evolving needs via email and phone support. These interactions include Canadian families navigating the challenges of ALGS and managing severe pruritus. In addition to these individual conversations and touchpoints, data and perspectives are gathered through a variety of methods: targeted family surveys and polls, structured focus groups in select geographic regions, and topic-specific discussions held within our private social media communities.

In a comprehensive family survey conducted by the ALGSA in September 2020, families across multiple countries—including Canadian participants—identified severe pruritus (itch) as the **#1 most impactful symptom of Alagille Syndrome** affecting daily life. This finding has been consistently reinforced through ongoing conversations, anecdotal reports, community support page conversations, and private support group discussions, where itch remains the most commonly mentioned and deeply distressing symptom.

The insights shared in this submission represent a broad cross-section of the ALGS community, including diverse demographics, disease severity, and treatment experiences. Our data reflects the lived experiences of patients and caregivers in Canada and worldwide, providing a rich, qualitative understanding of the burdens of pruritus and the hopes for more effective, accessible treatments.

3. Disease Experience

Alagille Syndrome (ALGS) is a complex, multi-system genetic disorder that profoundly impacts the day-to-day lives and emotional well-being of both patients and caregivers. While disease severity varies, most families describe the journey with ALGS as a constant balancing act between managing symptoms, navigating the healthcare system, and coping with an unpredictable future.

The most visible and burdensome aspect of ALGS—especially in childhood—is chronic liver disease. Symptoms like jaundice, severe pruritus (itching) contributing to extreme fatigue, loss of sleep, and discomfort, and malabsorption dominate daily life. Itch, in particular, is described by families as relentless, consuming, and life-altering. Children cannot sleep. They cannot concentrate in school or engage in normal activities due to the overwhelming need to scratch. Many routinely have open wounds leading to skin infections and skin damage from scratching until they bleed. Caregivers recount sleepless nights pacing hallways, bathing their children in oatmeal baths, trying numerous creams and ointments, medications, and alternative therapies—often with little or no relief. The mental health toll is staggering, with depression, anxiety, and feelings of helplessness and hopelessness common in both patients and parents.

The diagnostic journey adds another layer of trauma. Many patients experience long, complicated paths to diagnosis—misdiagnosed with Biliary Atresia or other conditions—often undergoing invasive procedures like the Kasai before Alagille Syndrome is finally identified. For adult patients, delayed diagnosis is common, with liver disease treated in isolation until a genetic connection is made years later through the diagnosis of a child or even a grandchild.

Beyond liver disease, ALGS often also involves the heart, kidneys, skeletal system, eyes, cerebrovascular and other areas like thyroid, parathyroid, ears, and more. Cardiac defects like pulmonary artery stenosis or Tetralogy of Fallot require invasive

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interventions—open-heart surgery, catheterizations, and frequent imaging. Kidney disease may progress to dialysis and transplant. Fragile bones lead to fractures that heal slowly, often causing lifelong skeletal challenges.

Nutritional challenges are another daily stressor. Malabsorption, poor growth, and feeding issues lead to intense pressure on caregivers to meet caloric goals that are many times unmanageable in the home. Families describe a relentless cycle of meal battles, weight checks, criticism from physicians when unrealistic goals are not met, and fear of feeding tubes as a signal of disease progression. Guilt, shame, self-blame, and helplessness are common as parents feel they are failing to keep their child healthy when in fact, they simply won't meet the goals due to the complexity of ALGS.

Perhaps most damaging is the long-term psychological impact of poor prognoses and life expectancy discussions delivered early in life. Many teens and adults share openly in our support pages that they were told or their parents were told—often in front of them as children—that they would not live past adolescence or survive without a transplant or other invasive interventions. This messaging leaves deep emotional scars, fueling lifelong anxiety, depression, and existential fear for patients and families that actually can pass down through generations.

Priorities for Management

The aspects most critical to control—ranked by their impact on quality of life—include:

1. **Pruritus:** Described as the most difficult and devastating symptom to deal with day to day. Effective, sustainable itch control would immediately improve sleep, mood, relationships, and mental health. Bylvay is providing relief and hope! More is needed for those who cannot access it. Effectively treating pruritus may contribute to a cascade effect of improvements in burden of disease, nutrition, sleep, emotional strain, and more.
2. **Liver function:** Preventing progressive liver damage is essential to avoiding transplant—a terrifying and risky last resort. Patients with vascular involvement face even greater transplant risks.
3. **Nutritional status:** Maintaining weight and growth is an exhausting, emotional battle for children and caregivers as well as adult patients. Fear of feeding tubes and shame over failing to meet weight milestones add extensive emotional burden.
4. **Cardiovascular health:** Heart defects demand constant surveillance and interventions. Each procedure or surgery carries risks that compound the family's fear of loss, impact of medical trauma, and a never-ending routine schedule of cardiac interventions, testing, and appointments.
5. **Bone health:** Fractures, slow healing, and long-term skeletal problems create chronic pain and mobility challenges. Many patients talk about the unexplained and undiagnosed bone pain that is often dismissed by physicians. Nutrition drastically impacts bone health as well as organ involvement including liver, kidney, thyroid, and more.

6. **Genetic counseling and reproductive health:** Families need support navigating the genetic risks, family planning, and reproductive options—all areas that are often overlooked but critical for long-term well-being.

Impact on Daily Life

The cumulative effect of ALGS is profound. Families live in survival mode—juggling endless appointments, managing complex medication regimens, coordinating school and work absences, and facing financial strain. Sleep deprivation, mental health crises, and social isolation are common. Siblings often carry secondary trauma, while marriages and family structures strain under the emotional and logistical weight.

While ALGS is medically complex, it is the *daily, relentless suffering from pruritus, emotional trauma, and uncertainty about the future* that patients and caregivers name as the most significant burdens. Any treatment that reduces these—especially effective itch relief—would radically change quality of life for these families.

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4. Experiences With Currently Available Treatments

Before the FDA approved Bylvay, patients relied on a regimen of multiple medications to manage itching—often starting with one drug and then introducing additional or alternative medications based on effectiveness until all lines are exhausted. The first-line treatment has typically been Rifampin, an old antibiotic originally used for Tuberculosis. However, its ability to alleviate pruritus is minimal, if at all, and usually only shows some benefit when combined with hydroxyzine, cholestyramine, naltrexone, or ursodiol. Patients often worry about the long-term effects of Rifampin which are not widely discussed with medical providers and patients are often on this antibiotic for 10+ years or until liver transplant. The medications discussed here, while cheaper for patients, are very ineffective overall. Patients and caregivers voice their desperation regularly for improved treatments within the support pages.

Desperate for relief, patients and caregivers frequently experiment with various non-prescription remedies, including lotions for soothing effects, as well as supplements like melatonin, ginkgo biloba, and oatmeal bath treatments or over the counter medicines like benadryl. Unfortunately, even when combined, these approaches rarely provide significant relief. In cases where severe pruritus remains unmanageable despite medical and supportive interventions, patients may be evaluated for liver transplant or other invasive surgical procedures to mitigate their daily suffering.

Managing these medications presents additional challenges, including complex dosing schedules, timing around other prescriptions, food intake restrictions, refrigeration requirements, and the need to coordinate with school or work routines. Beyond medications, vitamins, supplements, topical treatments, and surgical interventions such as internal or external biliary diversion or liver transplantation may be considered depending on disease severity, the intensity of itching, and overall quality of life. However, liver transplantation does not cure Alagille Syndrome. It is an extremely invasive procedure with significant risks and long-term maintenance, including a high likelihood of complications or failure, particularly in patients with vascular abnormalities associated with Alagille Syndrome, which can increase the risk of fatal outcomes.

Along with the regimen described above, CADTH's positive recommendation response to Livmarli in 2024 has further improved treatment options. However, we feel strongly that by providing a positive recommendation response for Bylvay would give patients and their families the flexibility to choose the option that best suits their circumstances, as some patients may respond better to one but not the other. Or, some patients may initially respond well. but experience a loss of efficacy over time, making the alternative a necessary option. Further, the difference in how the treatments are administered (e.g., oral capsules vs. liquid formulations) may mean that one might be a better fit for certain individuals.

Patient Testimonies

"Our son started itching around 5 to 6 months. It got really bad at 7 months. He was already taking ursodiol and rifampin and another medication was added in at 7 months. I found it got worse when we were in heat. Keeping him cool was key for us. Our son was transplanted at 21 months of age."
~Mom of son with ALGS, Ontario

I'm glad to hear they (Ipsen) came out with a capsule. My son has hated liquid medication (and taste) since he was little. He is now almost 14 yrs old. I'm interested to hear what others say as well about Bylvay. We did try Livmarli but he wouldn't take a dose of it because it was liquid"
~Mom of son with ALGS, Wisconsin, USA

"The most annoying thing is the itching of his skin that makes my daughter and her mother not sleep at night. Doctors have suggested she take hydroxyzine, but this drug wasn't effective."
~Dad of daughter with ALGS, Iran

"My 3 month old just keeps getting more and more jaundiced. He basically looks green, he's so yellow now. He's SO itchy. He scratches and rubs his face until it bleeds. He pulls at his ears and turns his head side to side so quickly to rub the back of his head. He's on the maximum safe dose of ursodiol for his age/weight. I'm hopeful he can start a medication soon for itching but he's only 3 months old and may be limited in options"
~Mom of son with ALGS, Pennsylvania, USA

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"My 22 month old little girl was diagnosed with ALGS in March 2023. She was managing ok without medication, however over the past month or so her itching has gotten to the point where it is impacting her days and her sleep, and mine. She started ursodiol twice a day, rifampicin once a day, and phenobarbital just before bed. I've noticed that the past week or so I'm really struggling mentally. I think this is because it feels real now. I was secretly hoping it would be mild. I often feel alone as it is such a rare condition. My daughter is refusing all medication now, so it is also quite distressing having to hold her down to give her medications. I feel so cruel. Any advice on how to make it easier for her to take medications would help."
~Mom to daughter with ALGS, United Kingdom

In regard to current treatment effectiveness:
Post by Parent in Private International ALGSA Support Page
By mom of son with ALGS in Australia - March 14, 2024
"Trialing cholestyramine for my son's itch. Any side effects I need to be aware of?"

Responses:
"Just have to make the timing between other meds and cholestyramine. My son has been taking it for a year now. We give it around 21:00h because it tends to bother his stomach."
~Mom to son of ALGS, United Kingdom

"Couldn't get passed the constipation"
~Mom to daughter with ALGS, Illinois, USA

"It worked okay for my son in combination with other drugs for about a year and a half. Now, he's on odevixibat and that has worked wonders for him"
~Mom of son with ALGS, Australia

5. Improved Outcomes

Patients and caregivers in the Alagille Syndrome community are desperately seeking treatments that can provide *meaningful* and *consistent* relief from severe pruritus—something that existing therapies often fail to deliver. The ideal improvement would be a treatment that significantly reduces itch intensity and frequency, allowing patients—especially children—to sleep through the night, focus in school, and participate in daily activities without constant distraction or distress. Caregivers often describe severe itching as *debilitating*, affecting every aspect of family life, including sleep, mental health, relationships, and employment not just for the patient, but for the whole family.

A new treatment that achieves sustained itch relief without the burdens of complex medication schedules or severe side effects would be life-changing. Families hope for an option that:

- Works reliably for *most* patients
- Reduces the need for multiple medications
- Comes in an easy-to-administer form (liquid or dissolvable tablet)
- Avoids major side effects like sedation, liver strain, or serious infections
- Minimizes disruption to school, work, and family schedules

Improved quality of life would be profound. Children could sleep, play, and learn without being overwhelmed by constant discomfort. Parents and caregivers would face less emotional distress, fewer sleepless nights, and fewer missed days at work or school. The mental health toll on entire families could be drastically eased. There is also hope that a new therapy could reduce the need for invasive, scary, and risky interventions like liver transplant. Preserving patients' futures and lowering long-term healthcare risks and costs is a priority for patients and caregivers.

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When weighing trade-offs, families often balance potential relief against the risks of side effects, the burden of complex regimens, and the financial strain of expensive medications or procedures. They are often willing to accept mild side effects or minor inconveniences *if* the treatment truly improves itching and restores some normalcy. However, treatments that come with high risks—especially those that threaten survival, like transplant—or therapies that require frequent hospital visits or monitoring are seen as last-resort options. Accessibility (cost, insurance coverage, geographic access) will also heavily influence whether families feel a new treatment is truly viable.

Ultimately, the Alagille Syndrome community wants a treatment that offers *real, sustainable relief* with fewer daily burdens—one that gives patients back their childhoods and families back their peace of mind.

Patient Testimonies
"My son is covered in cuts and bruises and is very unhappy. His sleep is non-existent and he spends his days scratching and being miserable. He has lost his spark."
~Mom of son with ALGS, Toronto

"My son started Bylvay (odevixibat) at the end of last year and it has done wonders for him. He turned 3 last July. He used to be on 9 different medications and since starting odevixibat, he is now down to 5 with the possibility of dropping another one in 6 months if his bloods continue to show positive signs. The capsule was easy. I just opened it up and put it on a spoon of yogurt"
~Mom to son with ALGS, New South Wales

"My son has been on Odevixibat for 9 months now. We saw zero side effects and from my understanding are less than those with other drugs"
~Mom to son with ALGS, North Carolina, USA

Articles/Publications/Press Releases

Efficacy and safety of odevixibat in patients with Alagille syndrome (ASSERT): a phase 3, double-blind, randomised, placebo-controlled trial
Lancet Gastroenterol Hepatol 2024; 9: 632–45
Published online April 23, 2024
https://doi.org/10.1016/S2468-1253(24)00074-8
Phase 3 study published in The Lancet Gastroenterology & Hepatology reporting that odevixibat improved pruritus and reduced serum bile acids in patients with Alagille syndrome

*"**Findings***
Between Feb 26, 2021, and Sept 9, 2022, 52 patients were randomly assigned to receive odevixibat (n=35) or placebo (n=17), all of whom were included in the analysis sets. The median age was 5·5 years (IQR 3·2 to 8·9). 27 (52%) of 52 patients were male and 25 (48%) were female. The mean scratching score was elevated at baseline in both groups (2·8 [SD 0·5] for odevixibat vs 3·0 [0·6] for placebo). Mean scratching scores at weeks 21–24 were 1·1 (0·9) for odevixibat and 2·2 (1·0) for placebo, representing a least-squares (LS) mean change of –1·7 (95% CI –2·0 to –1·3) for odevixibat and –0·8 (–1·3 to –0·3) for placebo, which was significantly greater for odevixibat than for placebo (difference in LS mean change from baseline –0·9 [95% CI –1·4 to –0·3]; p=0·0024). Odevixibat also resulted in significantly greater reductions in mean serum bile acids from baseline versus placebo (237 µmol/L [SD 115] with odevixibat vs 246 µmol/L [121] with placebo) to the average of weeks 20 and 24 (149 µmol/L [102] vs 271 µmol/L [167]; LS mean change –90 µmol/L [95% CI –133 to –48] with odevixibat vs 22 µmol/L [–35 to 80] with placebo; difference in LS mean change –113 µmol/L [95% CI –179 to –47]; p=0·0012). The most common treatment-emergent adverse events were diarrhoea (ten [29%] of 35 patients in the odevixibat group vs one [6%] of 17 in the placebo group) and pyrexia (eight [23%] vs four [24%]). Seven patients had serious treatment-emergent adverse events during the treatment period: five (14%) in the odevixibat group and two (12%) in the placebo group. No patients discontinued treatment and there were no deaths.
Interpretation
Odevixibat could be an efficacious non-surgical intervention to improve pruritus, reduce serum bile acids, and enhance the standard of care in patients with Alagille syndrome. Longer-term safety and efficacy data of odevixibat in this population are awaited from the ongoing, open-label ASSERT-EXT study."

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Bylvay (odevixibat) data shows sustained improvement in severe itch and serum bile acid levels in patients with PFIC and ALGS
GlobeNewswire
Press Release
November 18, 2024
https://www.globenewswire.com/news-release/2024/11/18/2982434/0/en/Bylvay-odevixibat-data-shows-sustained-improvement-in-severe-itch-and-serum-bile-acid-levels-in-patients-with-PFIC-and-ALGS.html
Data from the ASSERT-EXT study, an open-label extension of the ASSERT trial, showed sustained improvements in pruritus, serum bile acid levels, and growth parameters in patients treated with Bylvay for up to 72 weeks of treatment. The safety profile remained consistent with mild to moderate adverse events

"The sustained improvements we've seen in Bylvay-treated individuals living with Alagille syndrome are encouraging," said Dr. Nadia Ovchinsky, Chief, Division of Gastroenterology and Hepatology, Hassenfeld Children's Hospital at NYU Langone, New York. and principal investigator of the ASSERT trial. "These results not only show the potential to manage symptoms like pruritus, which can be extremely difficult for children and their parents to manage, but we're also seeing a consistent safety profile over the longer term with sustained tolerability."

In ASSERT-EXT, the open-label extension study (n=50) evaluating the long-term efficacy and safety of Bylvay in ALGS patients (ages 1-15.9 years) through 72 weeks (n=44), sustained improvements were observed in pruritus and sBA levels through 72 weeks.2 At week 72, 93 percent (n=28/30) of patients who received Bylvay throughout the 24 weeks ASSERT trial and 77 percent (n=10/13) of those who transitioned from placebo to Bylvay at week 24 experienced a clinically meaningful ≥1 point reduction in pruritus score. Reductions in sBA levels were also observed in patients treated with Bylvay for 72 weeks showing a mean reduction of 124 µmol/L in those who continuously received Bylvay and a mean reduction of 139 µmol/L in patients who transitioned from placebo to Bylvay. Mean changes from baseline were observed in height (8.2 cm) and weight (2.8 kg) on continuous Bylvay use and for patients who transitioned from placebo to Bylvay, height (10.7 cm) and weight (3.3 kg) mean changes were also reported.

Improvements in sleep were observed from weeks 24 to 72 across all four sleep parameters (n=43), including proportion of days seeing blood due to scratching, proportion of days needing help falling asleep, proportion of days needing soothing and daytime tiredness. Data supports the safety profile in the ASSERT clinical trial for Bylvay. Treatment emergent adverse event (TEAE) occurred in 18 percent (n=6/33) of patients who continuously received Bylvay and 41 percent (n=7/17) of patients who transitioned from placebo to Bylvay. Most adverse events were mild or moderate with diarrhea as the most common TEAE. One TEAE led to discontinuation."

Case Report: First Use of Odevixibat in Treating Alagille Patient
By Ryner Lai, MBBS
Rare Disease Advisor
April 18, 2023
"A genetic test was performed in August of the same year that revealed he had a heterozygous JAG1 mutation. His diagnosis was hence corrected to ALGS, making him ineligible to continue receiving odevixibat for PFIC. Nevertheless, his physicians continued to prescribe him odevixibat off-label, the dosage of which was changed multiple times according to his serum bile acids.
Within 4 days of starting odevixibat, the patient's mother reported that he was able to sleep through the night; in 2 weeks, his pruritus was mostly resolved and completely gone after 8 months. In addition, the patient's abdominal symptoms improved. The patient's improved clinical condition had a positive impact on the family's quality of life."

6. Experience With Drug Under Review

The availability of Bylvay in the United States and its presence in clinical trials worldwide, including in Canada, has provided a crucial treatment option for individuals with Alagille Syndrome suffering from severe pruritus. Through our interactions with patients and families in our support networks, we have observed firsthand the profound impact this medication has had on their quality of life.

Pruritus in Alagille Syndrome is relentless, leading to extreme discomfort, sleep deprivation, emotional distress, and a diminished ability to engage in daily activities. Families have shared that Bylvay has significantly eased this burden by:

- Dramatically reducing or eliminating pruritus, allowing patients to experience uninterrupted sleep and relief from constant scratching.
- Restoring energy levels for both patients and caregivers, improving overall family dynamics.

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- Enhancing physical health, including improved appetite, weight gain, and better hair and nail growth.
- Providing emotional relief by decreasing anxiety, depression, and feelings of guilt often associated with watching a loved one suffer.
- Lessening the overwhelming stress and helplessness families feel when no effective treatment options are available.

Families have relied in the past on various off-label medications and interventions that provided only temporary or partial relief. Many of these treatments carried unwanted side effects or were difficult to tolerate, leaving patients with few viable options. In contrast, Bylvay has demonstrated a significant and sustained improvement in pruritus, making it a far more effective solution than previous approaches.

Side effects reported within our community have primarily included mild to moderate gastrointestinal discomfort, such as cramping and diarrhea. However, most families note that these effects are temporary, typically improving within the first week or two of treatment. The benefit of itch relief overwhelmingly outweighs these initial side effects.

One of the most important aspects of Bylvay is the consistency of its effectiveness. Families who have attempted to stop treatment have seen a rapid return of severe pruritus, reinforcing its necessity for maintaining quality of life. Unlike other treatments that provided only minimal relief, Bylvay offers the hope of a more normal, less disruptive daily existence for both patients and their caregivers.

Ultimately, access to Bylvay represents more than just symptom management—it is a pathway to better sleep, improved mental and physical health, preservation of native liver function, and a significant reduction in the overall burden of Alagille Syndrome. For families who have struggled for years without adequate options, this medication provides a lifeline, restoring hope and stability in ways that were previously unattainable.

Ipsen Press Release
Bylvay® (odevixibat) data shows sustained improvement in severe itch and serum bile acid levels in patients with PFIC and ALGS
November 18, 2024
https://www.ipsen.com/press-releases/bylvay-odevixibat-data-shows-sustained-improvement-in-severe-itch-and-serum-bile-acid-levels-in-patients-with-pfic-and-algs-2982434/
"Assert-EXT Study in ALGS
"The sustained improvements we've seen in Bylvay-treated individuals living with Alagille syndrome are encouraging," said Dr. Nadia Ovchinsky, Chief, Division of Gastroenterology and Hepatology, Hassenfeld Children's Hospital at NYU Langone, New York. and principal investigator of the ASSERT trial. "These results not only show the potential to manage symptoms like pruritus, which can be extremely difficult for children and their parents to manage, but we're also seeing a consistent safety profile over the longer term with sustained tolerability."
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Patient testimonies:
"Prior to Odelixivat, my son's itch was uncontrollable. He scratched throughout the day, especially bad at bedtime. He would wake several times throughout the night and wasn't sleeping well at all. Since Odelixivat, our son rarely itches and he is sleeping through

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the night for the first time ever in his life. It has improved the quality of his life in many ways."
~ Mom to son with ALGS, Kansas, USA

7. Companion Diagnostic Test

Diagnosis of Alagille Syndrome can vary per institution, physician, and geographic area. Patient and caregiver experiences related to diagnosis also vary. Doctors can diagnose ALGS through identification of clinical features or genetic testing.

8. Anything Else?

No

Appendix: Patient Group Conflict of Interest Declaration

To maintain the objectivity and credibility of the CADTH reimbursement review process, all participants in the drug review processes must disclose any real, potential, or perceived conflicts of interest. This Patient Group Conflict of Interest Declaration is required for participation. Declarations made do not negate or preclude the use of the patient group input. CADTH may contact your group with further questions, as needed.

1. Did you receive help from outside your patient group to complete this submission? If yes, please detail the help and who provided it.

NO

2. Did you receive help from outside your patient group to collect or analyze data used in this submission? If yes, please detail the help and who provided it.

NO

3. List any companies or organizations that have provided your group with financial payment over the past 2 years AND who may have direct or indirect interest in the drug under review.

Table 1: Financial Disclosures

Check Appropriate Dollar Range With an X. Add additional rows if necessary.

Company	$0 to 5,000	$5,001 to 10,000	$10,001 to 50,000	In Excess of $50,000
IPSEN				X
MIRUM				X
TRAVERE THERAPEUTICS			X	

I hereby certify that I have the authority to disclose all relevant information with respect to any matter involving this patient group with a company, organization, or entity that may place this patient group in a real, potential, or perceived conflict of interest situation.

Name: ROBERTA SMITH

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Position: PRESIDENT
Patient Group: ALAGILLE SYNDROME ALLIANCE
Date: MARCH 16, 2025

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CADTH Reimbursement Review

Clinician Group Input

CADTH Project Number: SR0884-000
Generic Drug Name (Brand Name): Odevixibat (Bylvay)
Indication: Bylvay (odevixibat) is indicated for the treatment of Alagille's Syndrome
Name of Clinician Group: Canadian Paediatric Hepatology Research Group (CPHRG) committee of the Canadian Association for the Study of the Liver (CASL)
Author of Submission: Susan M. Gilmour

1. About Your Clinician Group

CASL is a non-profit organization that seeks to eliminate liver disease through research, education and advocacy. Our members are experts on liver disease in Canada: hepatologists, gastroenterologists, pediatricians, surgeons, radiologists, researchers, nurses, trainees, community advocates, and patients and family partners. The Canadian Paediatric Hepatology Research Group (CPHRG) is a committee within CASL which encompasses all the specialist paediatric hepatologists in Canada. Dr. Carolina Jiminez is the Chair of the CPHRG.

https://hepatology.ca

2. Information Gathering

The data and information presented here are gathered from a review of the published literature about Alagille's Syndrome (ALGS) and Odevixibat and attendance at conferences and abstract presentations about Odevixibat. Further the information is based on collective expert opinion within the CPHRG drawn from decades of experience managing patients with Alagille's Syndrome.

3. Current Treatments and Treatment Goals

Alagille's Syndrome (ALGS) is an autosomal dominant, multisystem disease, characterized by mutations in the JAG1 and NOTCH2 signaling pathways. This results in defective bile duct morphogenesis and impaired angiogenesis; also abnormalities in skeletal, ocular, cardiovascular and kidney development. The incidence is approximately 1:30-50,000. This is likely an underestimate due to the lack of genetic testing in earlier epidemiologic studies as well as potential underdiagnosis of ALGS. Approximately 60% of these gene mutations are de novo with the remaining 40% inherited from a parent. The main liver clinical features of ALGS include, cholestasis, jaundice, xanthomas and pruritus with symptoms typically appearing in infancy and early childhood. In multicentre observational studies liver transplant occurs in up to 40% of patients in their early years. Pruritus was noted to be one of the primary indications for liver transplantation.

Liver treatment strategies in ALGS aim to manage the cholestasis, liver failure and portal hypertension. Specifically, the cholestasis complications include malnutrition, fat soluble vitamin deficiency and pruritus. There are currently no curative medical therapies for ALGS and the treatment paradigm described below is supportive and aims to ameliorate symptoms and to try to delay the need for liver transplant, however no therapies targe the underlying disease mechanism of bile duct paucity.

The management strategies described are all standard of care in Canada. There are no practice guidelines that outline this treatment paradigm due to the rarity of the disease and limited published data that meet the standards for a guideline, however multiple review articles encompass this information.

Nutritional Management

Children with cholestasis, including ALGS require approximately 125% of the recommended daily allowance of calories and may need more for catch up growth. This is typically secondary to decreased oral intake and fat malabsorption. Medium chain triglyceride-rich foods are encouraged for ease of absorption, as well as other calorie dense foods. In children not being able to meet their caloric demands, tube feeding (nasogastric or via gastrostomy) is often required, especially in the context of progressive liver disease.

Supplementation with fat-soluble vitamins is crucial. To aid with adherence and cost, cholestasis-specific formulations are available in Canada (e.g., DEKAs) via the special access pharmacy and are the preferred strategy for supplementing vitamins. However, individual vitamin supplementation is acceptable if generic multivitamin preparations are the only available option.

Management of Pruritus

Pharmacological treatments

Treatment of cholestatic pruritus requires a stepwise approach. All the following medications are used off-label. Antihistamines are initiated first and are typically not effective but can be considered in mild cases and to augment sleep. Ursodeoxycholic acid promotes bile excretion rendering it more hydrophilic. Due to its attractive safety profile, it is typically used as early in the management of cholestasis. Cholestyramine, a bile salt-binding agent may also be considered. Cholestyramine decreases bile acid pool size by binding bile salts in the small intestine and hence preventing their reabsorption. However, poor palatability and interference with absorption of other drugs (specifically fat-soluble vitamins) limits its use and it is almost never used in clinical practice. Rifampin is much preferred to treat pruritus instead of cholestyramine. Through its enzymatic induction in the liver, it is thought to increase the metabolism of pruritogens. Opioid antagonists such as naltrexone, are sometimes added to the regimen if pruritus persists and may provide modest additional benefit. Opioid withdrawal symptoms which may occur in one-third of patients limits its use in clinical practice. Lastly, sertraline, a selective serotonin reuptake inhibitor (SSRI), has been used in refractory cases. Its mechanism of action is poorly understood. Limited pediatric studies support its use as adjunctive therapy intractable cholestatic pruritus and it is infrequently used in clinical practice.

Data from studies and observational registries support a treatment goal of interrupting the bile acid enterohepatic circulation in ALGS to alleviate pruritus, and more importantly to improve long-term liver disease outcomes and perhaps postpone and prevent the need for liver transplantation.

4. Treatment Gaps (unmet needs)

4.1. Considering the treatment goals in Section 3, please describe goals (needs) that are not being met by currently available treatments.

The treatment paradigm for cholestatic pruritus described above falls short for many patients with ALGS-associated cholestatic liver disease. Patients with even mild to moderate cholestasis typically suffer from severe, debilitating pruritus. Ursodeoxycholic acid is used as a choloretic and a treatment for cholestasis but has no impact on pruritus. Antihistamines are rarely effective as anti-

pruritics, cholestyramine is unpalatable, and although rifampin does provide some symptomatic relief for pruritic patients, it is usually ineffective in substantially ameliorating or eradicating pruritus. Sertraline and naltrexone provide marginal additional benefit, if at all. Therefore, current medical treatment paradigms for pruritus are insufficient for many cholestatic patients with ALGS. Given that pruritus is published as being one of the primary indications for liver transplantation, between 50-75% of ALGS patients end up requiring liver transplantation. Liver transplantation is, of course, associated with significant mortality and morbidity from major surgery and lifelong immune suppression.

Place in Therapy

5.1. How would the drug under review fit into the current treatment paradigm?

As described above, many patients with ALGS and cholestatic pruritus have inadequately treated pruritus with standard of care (off-label) medical therapy. Odevixibat would be added to the current toolkit of available medical therapies. Odevixibat would be used in combination with the other available medications. None of the currently available therapies interrupt enterohepatic circulation of bile acids and lower serum bile acids by blocking bile acid uptake in the ileum. It is true that cholestyramine is a bile acid-binding resin and can also reduce bile acid return to the liver, however it is not as efficacious as blocking the intestinal bile acid transporter and more importantly it is unpalatable, limiting its utility. As a result cholestyramine is rarely used in clinical practice.

Odevixibat treats cholestatic pruritus which is very debilitating for patients. Pruritus disrupts sleep for children and the whole family with wide-ranging impacts on health-related quality of life. Odevixibat is an effective symptomatic treatment. The data demonstrating that registry patients compared to those treated with iBAT inhibitors which lower serum bile acid levels is associated with improved native liver survival, suggests that odevixibat has an important role as a treatment for cholestasis associated with ALGS to delay or prevent liver transplantation. Odevixibat would be used in patients with ALGS who have persistent pruritus on ursodexycholic acid, antihistamines and rifampin and would also be considered in patients with ALGS and cholestasis, even if their pruritus

is adequately controlled with existing medications. Odevixibat would be added into the treatment plan (rather than as a replacement for these other medications). It is possible that some patients may be able to wean off some of the standard medications once they are established on Odevixibat. Naltrexone and sertraline are rarely offered in clinical practice due to very limited efficacy and tenuous safety profiles and therefore we would NOT recommend that these be attempted prior to offering Odevixibat.

5.2. Which patients would be best suited for treatment with the drug under review? Which patients would be least suitable for treatment with the drug under review?

Patients with ALGS and cholestatic pruritus, which is persistent on standard of care medical treatment would be eligible for treatment. Patients with ALGS and cholestatic liver disease and adequately controlled pruritus would also be eligible for treatment to improve liver disease outcomes and prevent or delay the need for liver transplantation. Since the mechanism of action of Odexivibat is to lower serum bile acids, it is reasonable to anticipate that patients with elevated serum bile acids are most likely to respond to treatment. Patients with moderate to severe pruritus, as determined by clinician evaluation and parent/caregiver/patient report, would have the greatest need.

The diagnosis of ALGS generally requires a phenotypic diagnosis (consistent biochemistry, clinical multi-system constellation and liver histology) and in addition, but not necessarily, a confirmatory genetic diagnosis. These criteria have been accepted by the Pediatric Hepatology community for diagnosis and even for entry to global registries.

5.3 What outcomes are used to determine whether a patient is responding to treatment in clinical practice? How often should treatment response be assessed?

The primary outcomes in the clinical trials of ALGS patients were patient-reported assessments of pruritus severity and serum bile acids (if accessible in the jurisdiction). The exact tool to assess

pruritus in the trials is not feasible in clinical practice as it requires twice daily scores over 2 weeks. In clinical practice pruritus severity is assessed by asking the patient/family about severity of pruritus, sleep disturbance and then examining the skin for excoriations. The physical examination can be scored according to the Clinician Scratch Scale and this was also included in the clinical trials. Serum bile acid levels can also be used, however in clinical practice this is not done routinely due to cost and logistics as this test is often sent to specialized laboratories and is not readily available in all gastroenterology practice settings.

A clinically meaningful response would be patients/families reporting an improvement in pruritus, improvement in sleep duration which can be objectively measured by asking how often the child wakes at night or by documenting improvements in skin excoriations.

5.4 What factors should be considered when deciding to discontinue treatment with the drug under review?

The most likely reason to discontinue treatment with Odevixibat would be if a ALGS patient's liver disease progresses and they undergo liver transplantation. Patients with ALGS can be continued on Odevixibat while waiting for liver transplantation as it can improve pruritus and quality of life.

Other factors that should be considering when deciding to discontinue treatment with Odevixibat would be treatment associated adverse events. The safety profile of the drug is generally good and data from the clinical trials are summarized below:

Patients, n (%)	Patients Treated With Odevixibat for ≥72 Weeks, n=52
Any TEAEs	47 (94%)
Serious TEAEs	6 (17%)
TEAEs leading to study treatment discontinuation	1 (2%)

The most important reported adverse effects in the clinical trials were gastrointestinal upset (diarrhea, abdominal pain) and increased ALT. It is certainly possible, in clinical practice, that gastrointestinal upset or increased ALT may lead to discontinuation, though based on the available clinical trial data, we do not expect this to affect large numbers of patients with ALGS.

5.5 What settings are appropriate for treatment with [drug under review]? Is a specialist required to diagnose, treat, and monitor patients who might receive [drug under review]?

Odevixibat should be prescribed and monitored by a pediatric gastroenterologist or hepatologist in a specialty clinic setting.

6. Additional Information

N/A

7. Conflict of Interest Declarations

To maintain the objectivity and credibility of the CADTH drug review programs, all participants in the drug review processes must disclose any real, potential, or perceived conflicts of interest. This conflict of interest declaration is required for participation. Declarations made do not negate or preclude the use of the clinician group input. CADTH may contact your group with further questions, as needed. Please see the *Procedures for CADTH Drug Reimbursement Reviews* (section 6.3) for further details.

1. Did you receive help from outside your clinician group to complete this submission? If yes, please detail the help and who provided it.

   No

2. Did you receive help from outside your clinician group to collect or analyze any information used in this submission? If yes, please detail the help and who provided it.

   No

3. List any companies or organizations that have provided your group with financial payment over the past two years AND who may have direct or indirect interest in the drug under review. **Please note that this is required for each clinician who contributed to the input — please add more tables as needed (copy and paste). It is preferred for all declarations to be included in a single document.**

Declaration for Clinician 1

Name: Susan M. Gilmour
Position: Professor Pediatrics
Director, Pediatric Liver and Intestinal Transplant program
University of Alberta
Stollery Children's Hospital

Date: 01-24-2025

☒ **I hereby certify** that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Table 1: Conflict of Interest Declaration for Clinician 1

	Check appropriate dollar range*			
Company	**$0 to $5,000**	**$5,001 to $10,000**	**$10,001 to $50,000**	**In excess of $50,000**
Mirum: Consultant Unrestricted Educational Grant		X (consultant)	X (clinical trial)	
Medison Consultant Unrestricted Educational Grant	X (consultant)			
Intercept Consultant		X (clinical trial)		

* Place an X in the appropriate dollar range cells for each company.

Declaration for Clinician 2

Name: Carolina Jiminez
Position: Associate Professor, Department of Pediatrics
Faculty of Medicine, University of Ottawa
Director of Liver Services
Chief, Division of Gastroenterology, Hepatology and Nutrition
Department of Pediatrics
Children's Hospital of Eastern Ontario

Date: January 31, 2025

☒ I hereby certify that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Table 2: Conflict of Interest Declaration for Clinician 2: NO FINANCIAL DISCLOSURES

Company	Check appropriate dollar range*			
	$0 to $5,000	$5,001 to $10,000	$10,001 to $50,000	In excess of $50,000
Add company name				
Add company name				
Add or remove rows as required				

* Place an X in the appropriate dollar range cells for each company.

Declaration for Clinician 3

Name: Simon Lam
Position: Clinical Assistant Professor
Gastroenterology, Hepatology & Nutrition
Alberta Children's Hospital

Date:

☒ I hereby certify that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Table 3: Conflict of Interest Declaration for Clinician 3: NO FINANCIAL DISCLOSURES

Company	Check appropriate dollar range*			
	$0 to $5,000	$5,001 to $10,000	$10,001 to $50,000	In excess of $50,000
Mirum: Consultant	x			
Medison Consultant		x		
Intercept Consultant		X (clinical trial)		

* Place an X in the appropriate dollar range cells for each company.

Declaration for Clinician 4

Name: Eve A. Roberts

Position: Professor Emerita, University of Toronto
Honorary Staff, Department of Paediatrics, The Hospital for Sick Children
Formerly: Director, Pediatric Hepatology, Division of Gastroenterology, Hepatology, and Nutrition

Date: 27 January 2025

☒ I hereby certify that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Table 4: Conflict of Interest Declaration for Clinician 4

	Check appropriate dollar range*			
Company	**$0 to $5,000**	**$5,001 to $10,000**	**$10,001 to $50,000**	**In excess of $50,000**
CADTH	X (Consultant)			
Mirum				X (Consultant)
Add or remove rows as required				

* Place an X in the appropriate dollar range cells for each company.

Declaration for Clinician 5

Name: Guillermo Costaguta

Position: Gastro-enterologie, Hepatologie and Nutrition pediatrique
CHU de Quebec – Universite Laval

Date: February 3, 2025

☒ I hereby certify that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Table 5: Conflict of Interest Declaration for Clinician 6: NO FINANCIAL DISCLOSURES

	Check appropriate dollar range*			
Company	**$0 to $5,000**	**$5,001 to $10,000**	**$10,001 to $50,000**	**In excess of $50,000**
Add company name				
Add company name				
Add or remove rows as required				

* Place an X in the appropriate dollar range cells for each company.

Declaration for Clinician 6

Name: Mar Miserachs

Position: Assistant Professor
Pediatric Gastroenterology, Hepatology and Nutrition
The Hospital for Sick Children
University of Toronto

Date: January 31, 2025

☒ I hereby certify that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Table 5: Conflict of Interest Declaration for Clinician 7: NO FINANCIAL DISCLOSURES

	Check appropriate dollar range*			
Company	**$0 to $5,000**	**$5,001 to $10,000**	**$10,001 to $50,000**	**In excess of $50,000**
Add company name				
Add company name				
Add or remove rows as required				

* Place an X in the appropriate dollar range cells for each company.

Declaration for Clinician 7

Name: Dhandapani Ashok
Position: Pediatric Gastroenterologist & Hepatologist
The Children's Hospital at London Health Sciences Centre
Associate Professor, Department of Pediatrics
Schulich School of Medicine and Dentistry, Western University

Date: January 31, 2025

☒ I hereby certify that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Table 5: Conflict of Interest Declaration for Clinician 8

	Check appropriate dollar range*			
Company	**$0 to $5,000**	**$5,001 to $10,000**	**$10,001 to $50,000**	**In excess of $50,000**

Add company name				
Add or remove rows as required				

* Place an X in the appropriate dollar range cells for each company.

Declaration for Clinician 8

Name: Andreanne Zizzo
Position: Associate Professor, Western University
Head, Division of Paediatric Gastroenterology & Hepatology
Chair, Resident Research Subcommittee
Director, PROGrS volunteer program
Children's Hospital, London Health Sciences Centre

Date: February 3, 2025

☒ I hereby certify that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Table 5: Conflict of Interest Declaration for Clinician 10: NO FINANCIAL DISCLOSURES

	Check appropriate dollar range*			
Company	**$0 to $5,000**	**$5,001 to $10,000**	**$10,001 to $50,000**	**In excess of $50,000**
Add company name				
Add company name				
Add or remove rows as required				

* Place an X in the appropriate dollar range cells for each company.

Declaration for Clinician 9

Name: Najma Ahmed

Position: Associate Professor Pediatrics, McGill University
Pediatric Gastroenterology and Hepatology
Montreal Children's Hospital

Date: January 31, 2025

☒ I hereby certify that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Table 5: Conflict of Interest Declaration for Clinician 11: NO FINANCIAL DISCLOSURES

Company	Check appropriate dollar range*			
	$0 to $5,000	$5,001 to $10,000	$10,001 to $50,000	In excess of $50,000
Mirum Pharmaceuticals		X (consultant)		
Add company name				
Add or remove rows as required				

* Place an X in the appropriate dollar range cells for each company.

Declaration for Clinician 10

Name: Mohit Kehar
Position: Pediatric Gastroenterologist and Hepatologist
Associate Professor
Division of Pediatric Gastroenterology, Hepatology and Nutrition
Children Hospital of Eastern Ontario, Ottawa

Date: February 3, 2025

☒ I hereby certify that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Table 5: Conflict of Interest Declaration for Clinician 16: NO FINANCIAL DISCLOSURES

Company	Check appropriate dollar range*			
	$0 to $5,000	$5,001 to $10,000	$10,001 to $50,000	In excess of $50,000
Mirum Consultant	X			
Add company name				
Add or remove rows as required				

* Place an X in the appropriate dollar range cells for each company

Declaration for Clinician 11

Name: Marie-Eve Chartier
Position: Pediatric Gastroenterologist-Hepatologist
Assistant Clinical Professor
Department of Pediatrics, Montreal University
Division of Gastroenterology, Hepatology and Nutrition
CHU Sainte-Justine

Date: 31-01-2025

☒ I hereby certify that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Table 5: Conflict of Interest Declaration for Clinician 17: NO FINANCIAL DISCLOSURE

	Check appropriate dollar range*			
Company	**$0 to $5,000**	**$5,001 to $10,000**	**$10,001 to $50,000**	**In excess of $50,000**
Mirum:		X (consultant)		
Ipsen	X (consultant)		X (clinical trial)	

Declaration for Clinician 12

Name: Orlee Guttman

Position: Clinical Associate Professor
GI Fellowship Program Director
Division of Gastroenterology, Hepatology and Nutrition
BC Children's Hospital

Date: January 30, 2025

☒ I hereby certify that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Table 5: Conflict of Interest Declaration for Clinician 20:

	Check appropriate dollar range*			
Company	**$0 to $5,000**	**$5,001 to $10,000**	**$10,001 to $50,000**	**In excess of $50,000**
Medison	X (consultant)			
Mirum	X (consultant)			
Add or remove rows as required				

* Place an X in the appropriate dollar range cells for each company.