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122 | INDIVIDUAL PRURITUS AND BILE ACID RESPONSES OVER TIME WITH ODEVIXIBAT TREATMENT: POOLED DATA FROM THE PHASE 3 ASSERT AND ASSERT-EXT STUDIES IN PATIENTS WITH ALAGILLE SYNDROME

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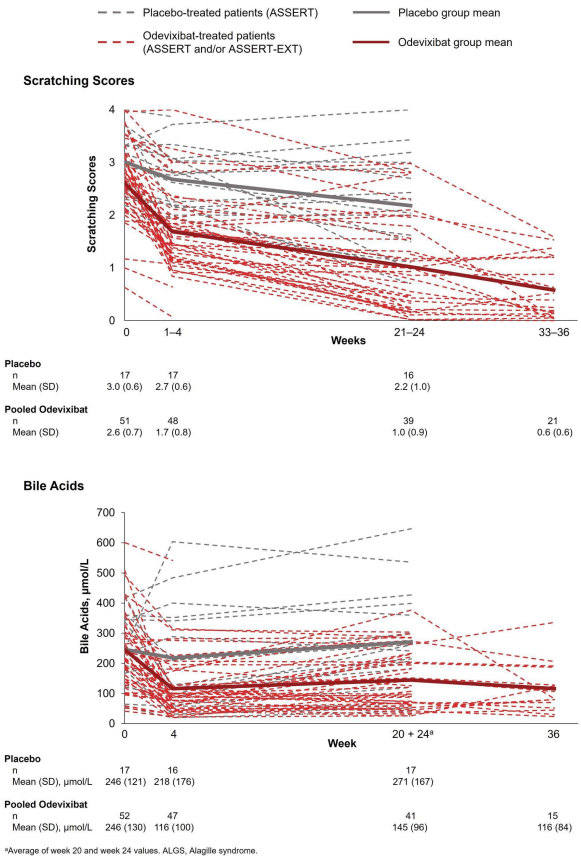
Background: Alagille syndrome (ALGS) is a rare, genetic, multisystem disorder in which cholestatic liver disease is common and that may include clinical manifestations of severe pruritus and elevated bile acids (BAs). The efficacy and safety of odevixibat, an ileal bile acid transporter inhibitor, were assessed in patients with ALGS in the phase 3 ASSERT and ASSERT-EXT trials. Using data from these studies, we analyzed the effects of odevixibat on pruritus and BAs over time. **Methods:** ASSERT (NCT04674761) was a randomized, placebo-controlled study that enrolled patients with ALGS who had a history of significant pruritus and elevated serum BAs. Patients were randomized 2:1 to odevixibat 120 μg/kg/day or placebo, respectively, and received treatment for 24 weeks. Patients who completed ASSERT could enter ASSERT-EXT (NCT05035030), an ongoing, 72-week open-label extension study in which all patients receive odevixibat 120 μg/kg/day. The primary endpoint in these studies was related to change in pruritus scores, evaluated using the PRUCISION observer-reported instrument (range, 0−4, with higher scores indicating worse symptoms). A secondary endpoint in both studies was change in serum BAs. Changes over time in scratching scores and BAs were analyzed in odevixibat-treated patients from ASSERT and/or ASSERT-EXT in a pooled analysis of data that spans from patients' first dose of odevixibat to a data cutoff date of September 9, 2022; data from patients who received placebo in ASSERT are presented for comparison. **Results:** At the data cutoff, 52 odevixibat-treated patients comprised the pooled population; 17 patients who received placebo in ASSERT subsequently received odevixibat in ASSERT-EXT. Odevixibat-treated patients had rapid reductions in mean scratching scores and BA levels that

Symbols: ♦, Poster of Distinction; ★, Foundation Award Recipient

were sustained over time; responses in individual patients are shown in the Figure. At the data cutoff date, treatment-emergent adverse events (TEAEs) were reported in 83% (43 of 52) of odevixibat-treated patients and in 71% (12 of 17) of placebo-treated patients. The most common TEAEs during odevixibat treatment were diarrhea (29%; 6% with placebo) and pyrexia (21%; 24% with placebo). Drug-related TEAEs occurred in 29% of odevixibat-treated patients (15 of 52) and in 18% of placebo-treated patients (3 of 17). In the odevixibat-treated group, the only drug-related TEAEs occurring in > 1 patient were diarrhea (6 patients, 12%) and abdominal pain, upper abdominal pain, and vomiting (each in 2 patients, 4% each). No odevixibat-treated patients had TEAEs leading to treatment discontinuation as of the data cutoff date. **Conclusion:** In patients with ALGS, odevixibat treatment for up to 36 weeks resulted in improvements in pruritus and reduced BA levels; these changes occurred rapidly, with effects sustained over time. Most TEAEs with odevixibat were related to diarrhea and were mild or moderate in severity.

Figure. Scratching Scores (A) and Bile Acid Levels (B) From Individual Patients With ALGS Who Received Odevixibat in ASSERT and/or ASSERT-EXT or Placebo in ASSERT



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123 | SPATIAL TRANSCRIPTOMICS IDENTIFIES IMMUNE EXPANSION OF SCAR REGIONS AND REDUCED HEPATOCYTE ZONATION IN LIVERS FROM PATIENTS WITH BILIARY ATRESIA

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Background: Multiple metabolic and inflammatory pathways have been associated with patient outcome in biliary atresia (BA), however, the spatial relevance of these pathways among BA and non-BA disease controls has not been well defined. In the present study, we overcome this gap in knowledge and define the hepatic spatial transcriptome in pediatric cholestasis. **Methods:** VISIUM Spatial transcriptomics was performed on frozen liver tissue obtained at the time of pediatric liver transplantation from 4 groups: 1) BA patients < 2 years of age (BA1, n = 3), 2) BA patients > 2 years of age (BA2, n = 4), 3) non-BA cholestatic patients (nonBA, n = 4), and 4) non-diseased pediatric donor liver (NL, n = 3). Published single-cell datasets were used to infer cell-type composition of hepatocyte and scar regions. Standard statistical tools were used to integrate and identify differential gene expression (DE), and tissue composition within and between samples. Metabolic pathways were modeled from gene expression using the compass algorithm. **Results:** BA1 patients had higher direct bilirubin level at the time of sample collection with median of 20.4 mg/dL (IQR 11.7-NA) compared to BA2 and nonBA groups with medians of 2.0 mg/dL (IQR 0.6-2.2) and 4.8 mg/dL (IQR 1.3-11.7) respectively ($p = 0.004$). This was associated with an increase in bile acid synthesis pathways and a trend towards greater cholangiocyte signature (Figure 1) in BA1 compared to BA2. In contrast, BA2 had higher immune infiltration in scar regions (Figure 1A) and arginine and proline metabolism. BA1 scars were most unique with 662 DE genes, whereas BA2 and nonBA scars had fewer than 50 DE genes. More specific comparison among the scar signatures of BA patients demonstrated distinct scar-associated clusters involved in angiogenesis and T cell activation in BA1 versus enriched processes of translation and peptide metabolic processes in BA2. Both BA groups showed reduced hepatocyte zonation as demonstrated by lower portal hepatocyte gene signature than nonBA and NL groups (Figure 1B). **Conclusion:** We identify distinct spatial transcriptomes in children with cholestatic liver disease that differ by etiology and disease severity. BA patients requiring earlier transplant (BA1) exhibited a higher bile acid metabolic signature and greater heterogeneity within the scar region than older BA patients (BA2). These findings help identify aberrant immune-metabolic patterns that may contribute to disease progression in BA.

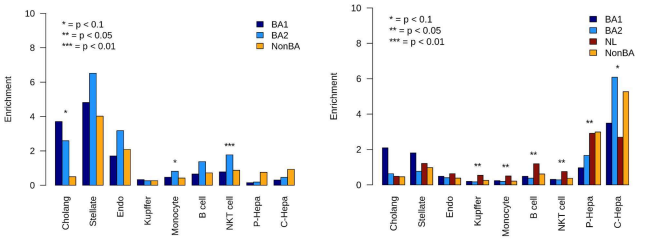

Figure 1. A. Enrichment for cell types in the scar region of diseased groups shows significantly increased NKT cell signature in BA2. **B.** Analysis within hepatocyte regions identified reduced peri-portal hepatocyte signature in BA groups whereas NL hepatocyte regions had increased expression of immune cell signatures.
C-Hepa – peri-central hepatocyte; Cholang – cholangiocyte; Endo – endothelial cell; NKT – natural killer T cells; P-Hepa – peri-portal hepatocyte.

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124 | STAT3 SIGNALING MEDIATES FXR AGONIST PROTECTION IN ACUTE CHOLANGIOPATHY MOUSE MODEL

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Background: Primary sclerosing cholangitis (PSC), a chronic cholangiopathy, results in cholestasis, inflammation, and stricturing of intrahepatic and extrahepatic bile ducts. Recently, we have shown that the transcription factor STAT3 mediated, in part, the protective role of the FXR agonist, GW4064, in parenteral nutrition

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