risk. During follow-up, increases in Ishak stage, hepatic collagen, and ELF were associated with progression to cirrhosis. Changes in NAS were not significant, but worsening lobular inflammation was associated with increased progression (HR 3.21; 95% CI 1.14, 9.04). After a median of 26.7 months (range, 0.1–42.3), 49 cirrhotic subjects (19.0%) experienced clinical events (ascites [n = 19], encephalopathy [n = 13], variceal hemorrhage [n = 6], newly-diagnosed varices [n = 4], ≥2-point increase in Child-Pugh score and/or MELD ≥ 15 [n = 6], death [n = 1]). Factors associated with disease progression included higher BL hepatic collagen and ELF, increases in these markers over time, and lack of improvement in Ishak stage (Table). Changes in NAS were not significant although the absence of improved lobular inflammation was associated with increased risk (HR 2.33; 95% CI 1.01–5.35).

Table: Factors Associated with Disease Progression in Patients with Advanced Fibrosis Due to NASH

| | Bridging Fibrosis (Progression to Cirrhosis) | | Cirrhosis (Adjudicated Clinical Events) | |
|---|---|---|---|---|
| Variable* | HR (95% CI) | P-Value | HR (95% CI) | P-Value |
| **Ishak stage** | | | | |
| Baseline 4 vs. 3 | 2.76 (1.52, 5.00) | <0.001 | N/A | N/A |
| Baseline 6 vs. 5 | N/A | N/A | 1.25 (0.68, 2.29) | 0.480 |
| No change or worsening[1] vs. improvement | N/A[2] | N/A | 9.63 (1.33, 69.81) | 0.025 |
| Worsening vs. no change or improvement | 44.01 (17.01, 114.33) | <0.001 | N/A | N/A |
| **Hepatic collagen**, % | | | | |
| Baseline | 1.27 (1.18, 1.36) | <0.001 | 1.07 (1.03, 1.11) | <0.001 |
| Change from baseline | 1.24 (1.19, 1.30) | <0.001 | 1.04 (1.01, 1.07) | 0.017 |
| **ELF** | | | | |
| Baseline | 3.13 (2.31, 4.22) | <0.001 | 2.37 (1.69, 3.31) | <0.001 |
| Change from baseline | 1.59 (1.18, 2.13) | 0.002 | 1.54 (1.10, 2.15) | 0.012 |
| **NAS** | | | | |
| Baseline ≤ 2 vs. 3–4 | N/A[3] | N/A | 0.99 (0.47, 2.10) | 0.99 |
| Baseline ≥ 5 vs. 3–4 | 1.64 (0.83, 3.27) | 0.16 | 0.78 (0.40, 1.54) | 0.48 |
| No change vs. improvement | 1.43 (0.71, 2.86) | 0.31 | 1.69 (0.84, 3.37) | 0.14 |
| Worsening vs. improvement | 1.20 (0.58, 2.51) | 0.62 | 0.87 (0.38, 1.98) | 0.74 |

N/A, not applicable.
*Changes from baseline adjusted for baseline value.
[1]Combined no change or worsening as reference group for subjects with cirrhosis (Ishak stage 5 or 6) at baseline because cirrhotic subjects with Ishak stage 6 fibrosis cannot have an increase in fibrosis stage.
[2]No subjects with bridging fibrosis at baseline who had Ishak improvement had a clinical event.
[3]No subjects with bridging fibrosis and a NAS ≤ 2 at baseline had a clinical event.

**Conclusions:** In patients with advanced fibrosis due to NASH, the primary determinant of disease progression is fibrosis and its change over time.

### GS-005
### Replacement of the murine common bile duct with a bioengineered conduit incorporating primary human cholangiocyte organoids

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**Background and Aims:** Treatment of common bile duct disorders such as biliary atresia is limited to liver transplantation or hepatojejunostomy due to the lack of suitable tissue for surgical reconstruction. Here we explore the potential of bioengineered biliary tissue consisting of human extrahepatic cholangiocyte organoids (ECOs) and biodegradable scaffolds for biliary reconstruction in vivo.
**Methods:** Primary human cholangiocytes were isolated by mechanical dissociation from deceased organ donors with ethical approval and informed consent (n = 8). Propagation of ECOs was achieved using our established protocol. Transcriptomic characterization was performed using the Illumina HumanHT-12v4 array. ECOs were seeded on Polyglycolic Acid (PGA) or densified collagen scaffolds. Biliary reconstruction was achieved by partially replacing the gallbladder wall with an ECO populated PGA-scaffold patch (ECO-patch; n = 8), or replacing a length of the native common bile duct with ECO populated collagen tubes (ECO-tubes) through end-to-end anastomosis (n = 4). All experiments were performed in immune compromised mice. Fibroblast-populated (n = 5, PGA; n = 4, collagen) or acellular scaffolds (n = 2, PGA) were used as negative controls. Biliary tree patency was confirmed using magnetic resonance cholangiopancreatography (MRCP) or cholangiogram.
**Results:** ECOs closely correlate with primary cholangiocytes in terms of transcriptomic profile (*r*:0.92), and functional properties (ALP, GGT, bile acid transfer). ECO-populated scaffolds form biliary tissue-resembling structures, maintain their functional properties (ALP, GGT) and marker expression (CK7, CK19, HNF1B). All ECO-transplanted animals exhibited prolonged survival (ECO-patch vs. acellular controls, $P = 0.0027$; ECO-tubes vs. fibroblasts, $P = 0.0082$; log-rank test). The transplanted cells integrated in the biliary epithelium, continued expressing biliary markers (CK7, CK19, HNF1B), exhibited ALP activity and a patent lumen. All reconstructions with fibroblasts failed, the biliary epithelium was replaced by fibrotic tissue and the lumen of the gallbladder or neo-bile duct was occluded.
**Conclusions:** We demonstrate that ECO-populated biodegradable scaffolds maintain key biliary characteristics and can reconstruct/replace parts of the biliary tree following transplantation. To our knowledge, this is the first demonstration for the application of regenerative medicine in the management of cholangiopathies and first report of an organ reconstruction using human primary cells expanded in vitro.

### GS-006
### EXPEDITION-I: efficacy and safety of glecaprevir/pibrentasvir in adults with chronic hepatitis C virus genotype 1, 2, 4, 5 or 6 infection and compensated cirrhosis

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