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Therapeutic Approaches to Cirrhotic versus Pre-Cirrhotic NASH

2nd Annual NASH Summit—Europe

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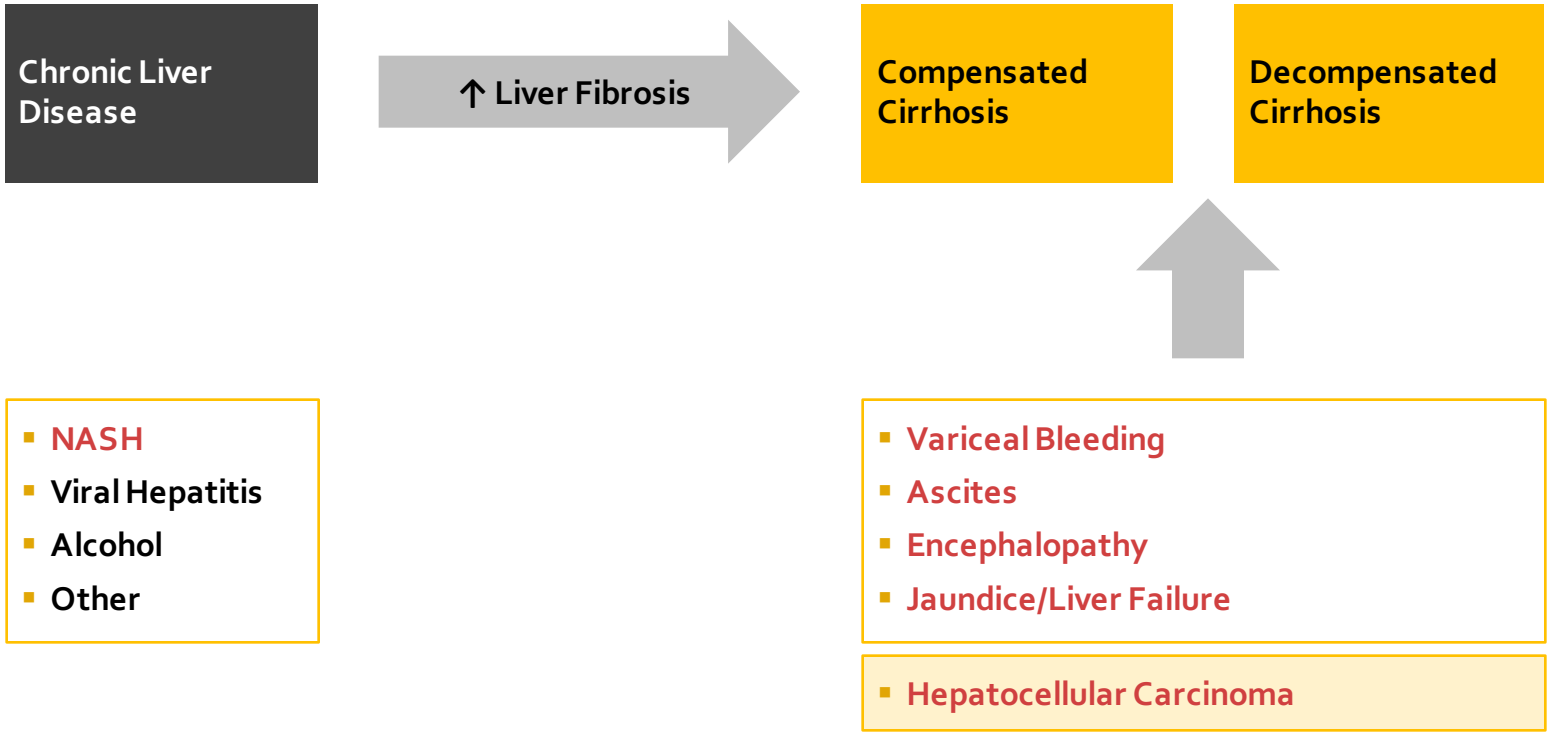
Disclosures

Presenter was previously full time employee of Galectin Therapeutics (CEO and CMO until June 2018), but currently owns no equity in company.

Chronic Liver Disease, Cirrhosis and its Progression



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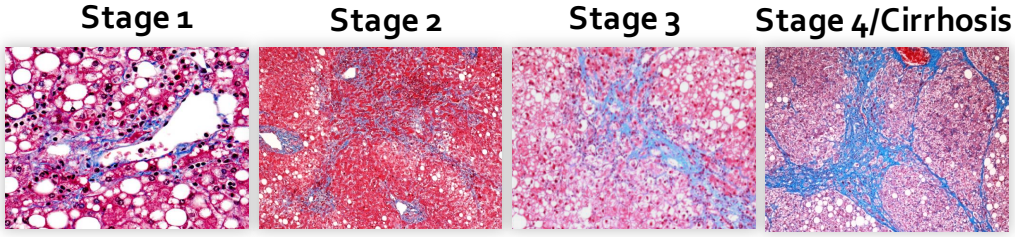
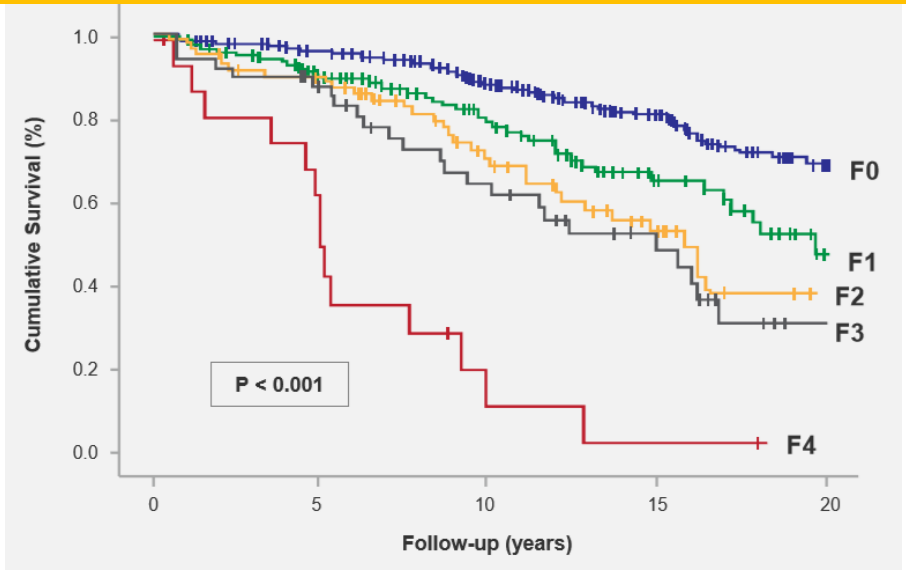
Fibrosis Stage Progression Associated with NASH



Survival Free of Liver Transplantation Based on Fibrosis Stage[1]



NASH and Fibrosis Stage

- Approximately one-third of patients with NASH will advance to Stage 3/4 fibrosis [2]
- An estimated 40% of NASH patients in the U.S. have a fibrosis stage of F2 or higher [3]
- NASH with advanced fibrosis carries the greatest risk of all-cause and liver-related mortality [2,4,5]

[1] Graphic taken from ICPT presentation May 2018 which re-graphs data from Angulo, et al. Gastroenterology 2015;149:389-397

[2] Caldwell, et al. Dig Dis 2010;28:162–168

[3] Estes, et al. Hepatology 2018;67:123-133

[4] Dulai, et al. Hepatology 2017;65:1557-1565

[5] Hagstrom, et al. J Hepatology 2017;67:1265-1273

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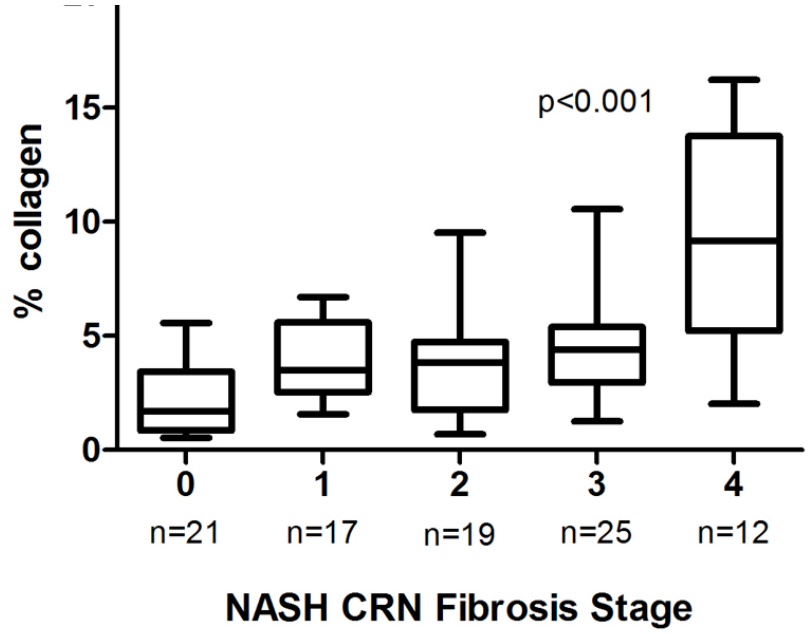
Percent Collagen in NASH Liver Biopsies per Stage of Fibrosis

Liver Biopsy Sirius Red Morphometry by Fibrosis Stage[1]



[1] Data from Goodman and Harrison

Collagen Accumulation in NASH

- The distribution of fibrosis in NASH is important in staging as well as the amount of collagen
- While there is an increase in the median percent collagen from stage 0 to 3, there is a great deal of overlap of values.
- In stage 4, or cirrhosis, there is a marked increase in the median amount of collagen and a very broad range.
- These and other published data show that progression of fibrosis after the development of cirrhosis is a critical element for development of complications of cirrhosis
- Better methods of quantifying fibrosis is required for early drug assessment

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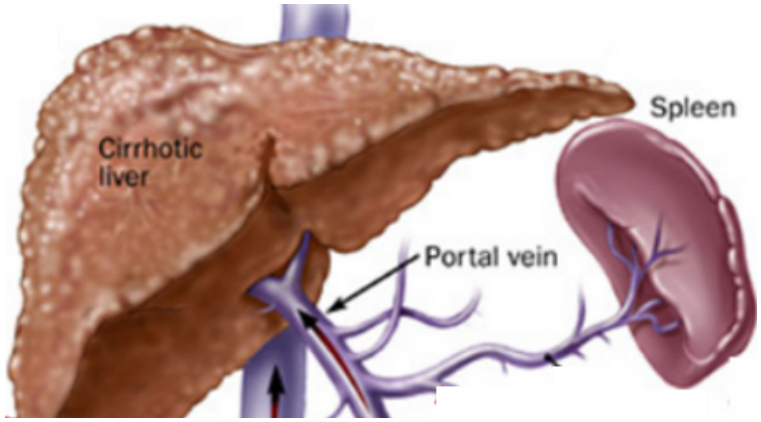
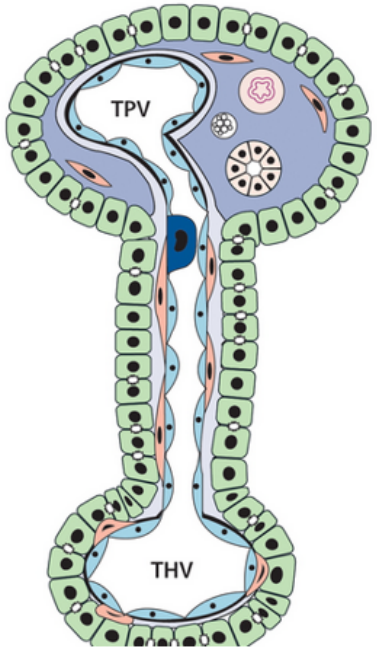
Portal Hypertension is a Major Driver of Decompensation

Increased pressure in the portal circulation is initiated by increased intrahepatic resistance to blood flow though the liver

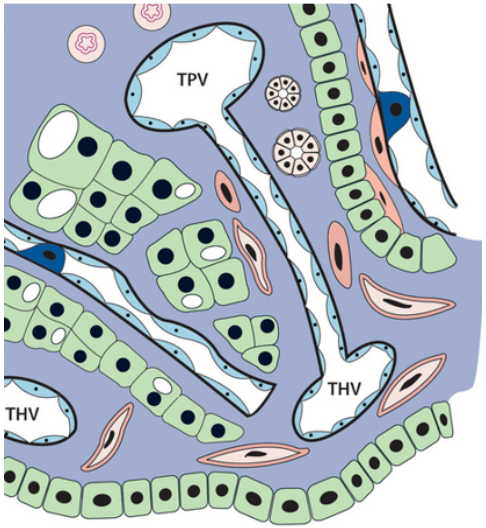


Multiple Contributors to Increased Intrahepatic Blood Flow Resistance in Cirrhosis

Normal Liver Acinar Unit



Distorted Architecture in Cirrhosis



- **Structural Components**
  - Scar tissue
  - Stellate cells
  - Regenerative nodules
  - Neoangiogenesis
  - Micro thrombosis
- **Non-Structural Components**
  - Nitric Oxide
  - Endothelin
  - Eiconsanoids
  - CO/others
  - "Endothelial Dysfunction"

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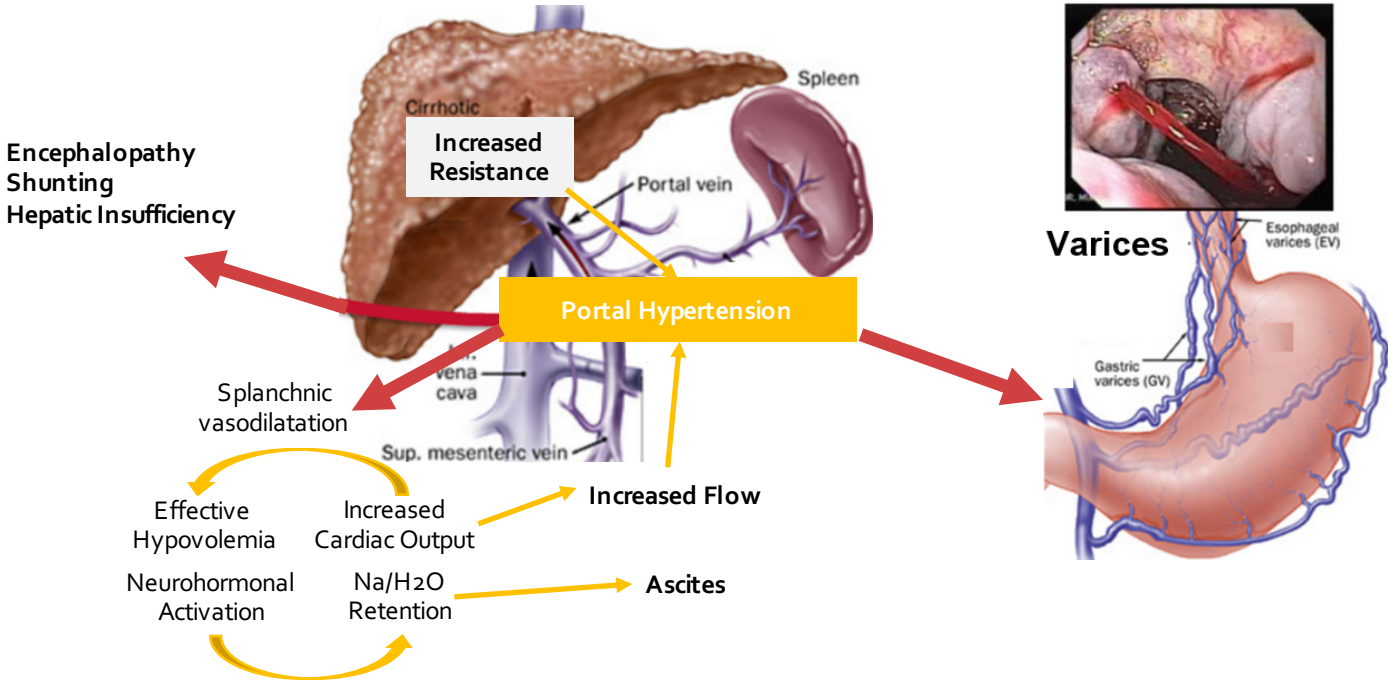
Cirrhosis Complications Center Around Increased Portal Vein Blood Pressure



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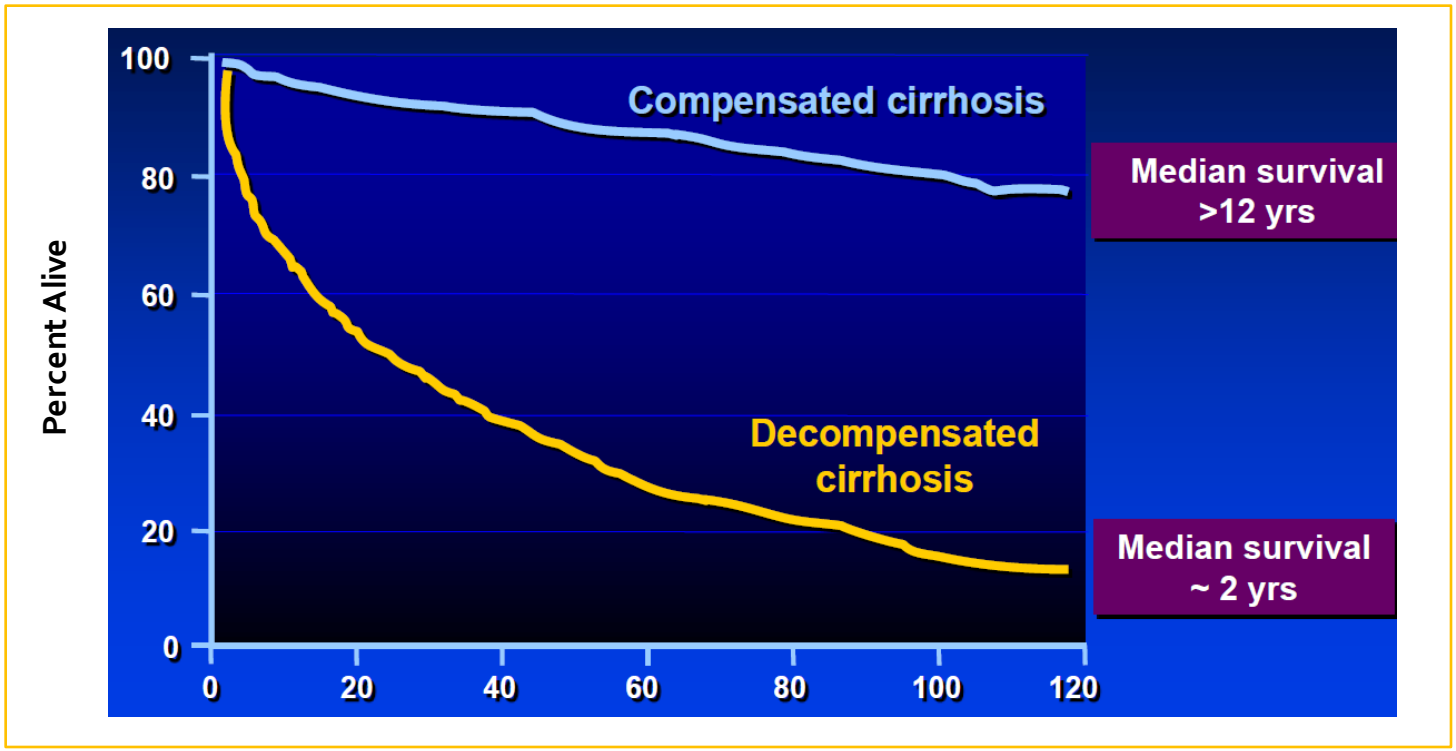
Survival Between Compensated and Decompensated Cirrhosis



D'Aminco et. Al., J Hepatol 2006;44:217 (Graphic borrowed from Dr. Guadalupe Garcia-Tso)

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Towards a Better Understanding of NASH Fibrosis/Cirrhosis Natural History

Fibrosis Severity as a Determinant of Cause-Specific Mortality in Patients With Advanced Nonalcoholic Fatty Liver Disease: A Multi-National Cohort Study

Eduardo Vilar-Gomez,[1,2,*] **Luis Calzadilla-Bertot**,[3,*] Vincent Wai-Sun Wong,[4] Marlen Castellanos,[5] Rocio Aller-de la Fuente,[6] Mayada Metwally,[7] Mohammed Eslam,[7] Licet Gonzalez-Fabian,[8] María Alvarez-Quiñones Sanz,[9] Antonio Felix Conde-Martin,[10] Bastiaan De Boer,[11] Duncan McLeod,[12] Anthony Wing Hung Chan,[13] Naga Chalasani,[1] Jacob George,[7] Leon A. Adams,[3,§] and Manuel Romero-Gomez[2,§]

Gastroenterology 2018;155:443–457

Simtuzumab Is Ineffective for Patients With Bridging Fibrosis or Compensated Cirrhosis Caused by Nonalcoholic Steatohepatitis

Stephen A. Harrison,[1] Manal F. Abdelmalek,[2] Stephen Caldwell,[3] Mitchell L. Shiffman,[4] Anna Mae Diehl,[2] Reem Ghalib,[5] Eric J. Lawitz,[6] Don C. Rockey,[7] Raul Aguilar Schall,[8] Catherine Jia,[8] Bryan J. McColgan,[8] John G. McHutchison,[8] G. Mani Subramanian,[8] Robert P. Myers,[8] Zobair Younossi,[9] Vlad Ratziu,[10] Andrew J. Muir,[2] Nezam H. Afdhal,[11] Zachary Goodman,[9] Jaime Bosch,[12,13] and Arun J. Sanyal,[14] for the GS-US-321-0105 and GS-US-321-0106 Investigators

Gastroenterology 2018;155:1140–1153

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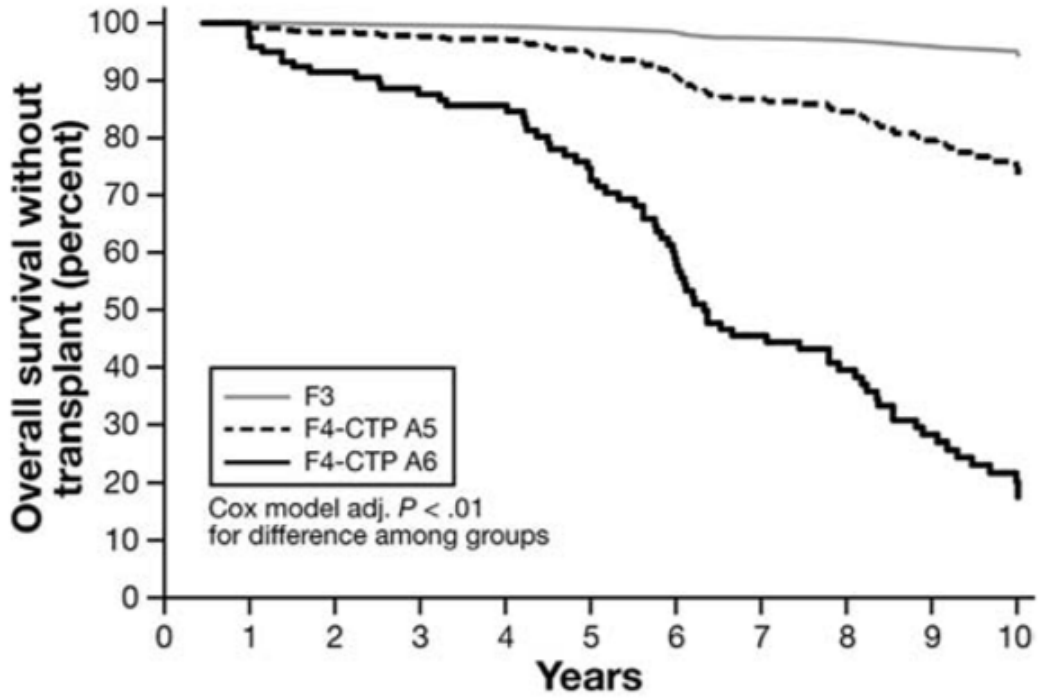
Adjusted Overall Survival Without Transplantation According to Fibrosis Stage and CTP



Multinational with patients recruited from tertiary treatment centers in Europe, Asia, Cuba, and Australia

- **A total of 458 subjects were included, of which 159 (35%) and 299 (65%) had bridging fibrosis and cirrhosis, respectively. Most cirrhotic patients were CTP-A5 (74%)**
- **Overall mean follow-up period was 5.5 years (range, 2.7—8.2 years)**

Vilar-Gomez, et. al., Gastroenterology 2018;155:443-457

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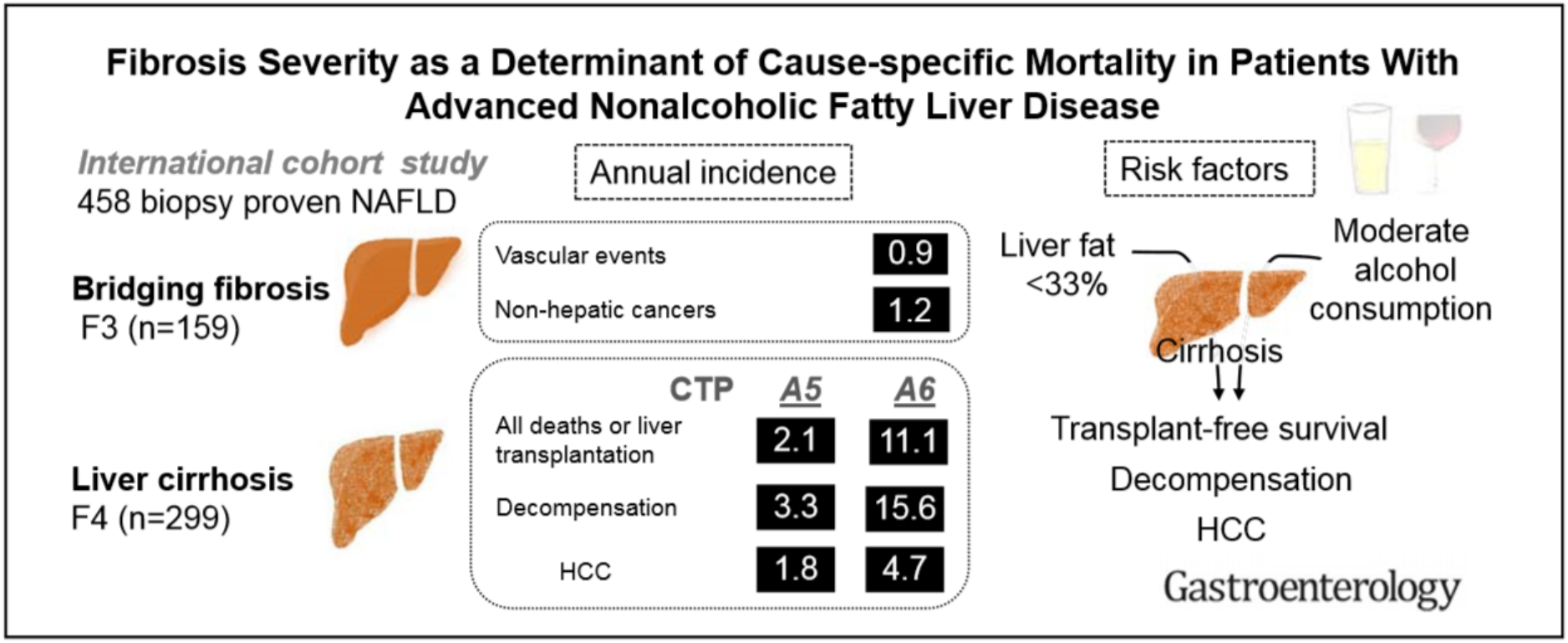
Data Summary Graphic



Vilar-Gomez, et. al., Gastroenterology 2018;155:443-457

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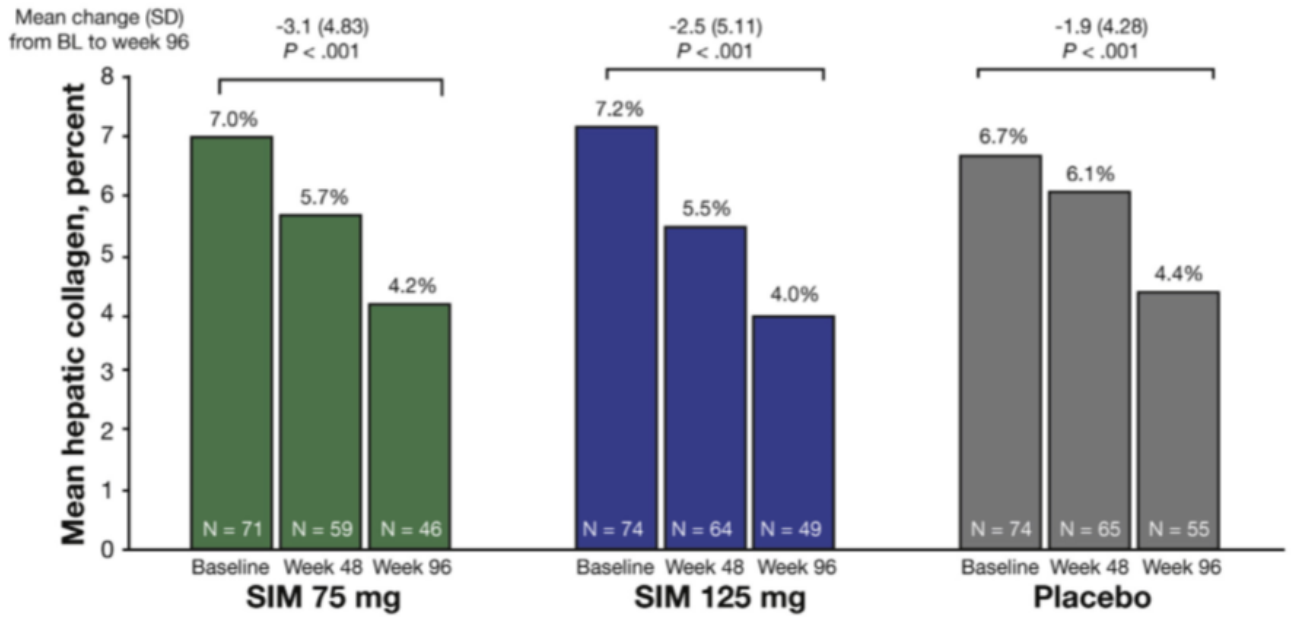
Phase 2b Results: Simtuzumab in NASH Patients with Bridging Fibrosis



Large, randomized controlled clinical trial (n=219) evaluating two doses of SIM after 48 and 96 weeks of therapy

- **Statistically significant reduction in liver collagen on biopsy over the course of the study in placebo group**
- **No difference between placebo and treatment groups in mean change in hepatic collagen by morphometry (primary endpoint)**

Harrison, et. al., Gastroenterology 2018;155:1140–1153

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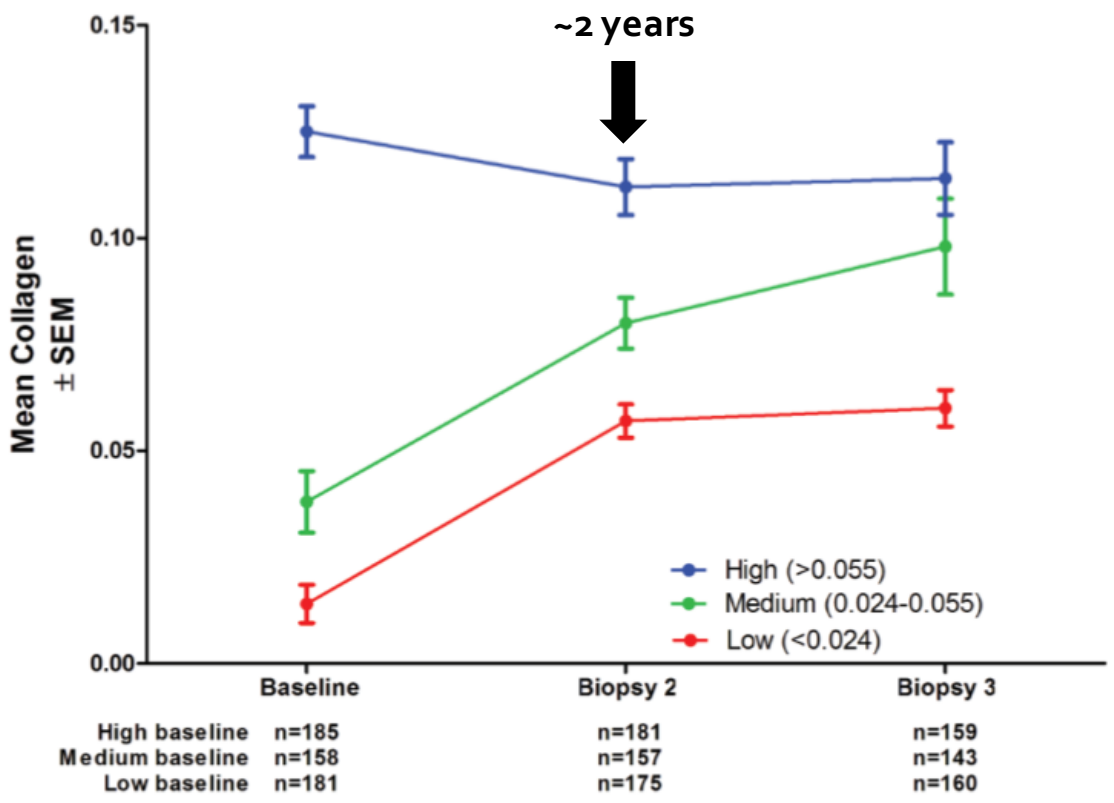
HALT-C Trial: Progression of Fibrosis in Chronic Viral Hepatitis C



Collagen content assessed by liver biopsy morphometry in patients with chronic viral hepatitis C

- **In lower and mid-range starting collagen %, there was a significant increase over 2 years**
- **The progression of fibrosis differs between chronic viral hepatitis C and NASH**

Goodman, et. al., Hepatology 2009;50:1738-1749

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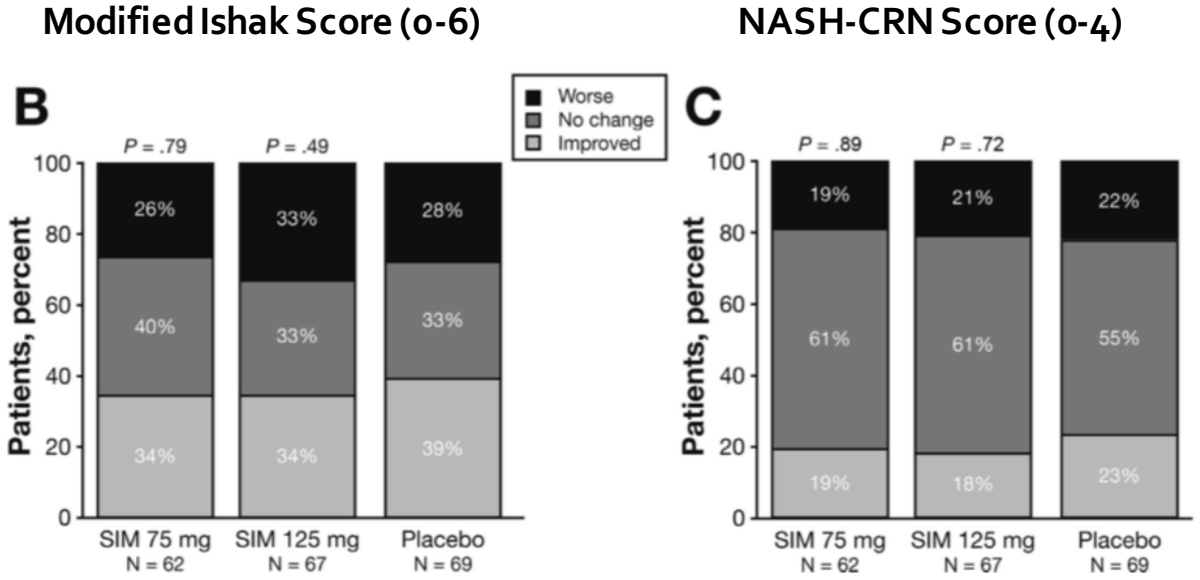
Phase 2b Results: Simtuzumab in NASH Patients with Bridging Fibrosis



Changes in fibrosis score

- **NASH-CRN score is currently required by regulatory agencies**
- **In placebo patients with median observation of 29 months, 23% had at least a one stage improvement in NASH-CRN score, and there was no difference in SIM groups**
- **20% of patients progressed to cirrhosis over mean observation of 30 months, using "histologic or clinical signs"**

Harrison, et. al., Gastroenterology 2018;155:1140–1153

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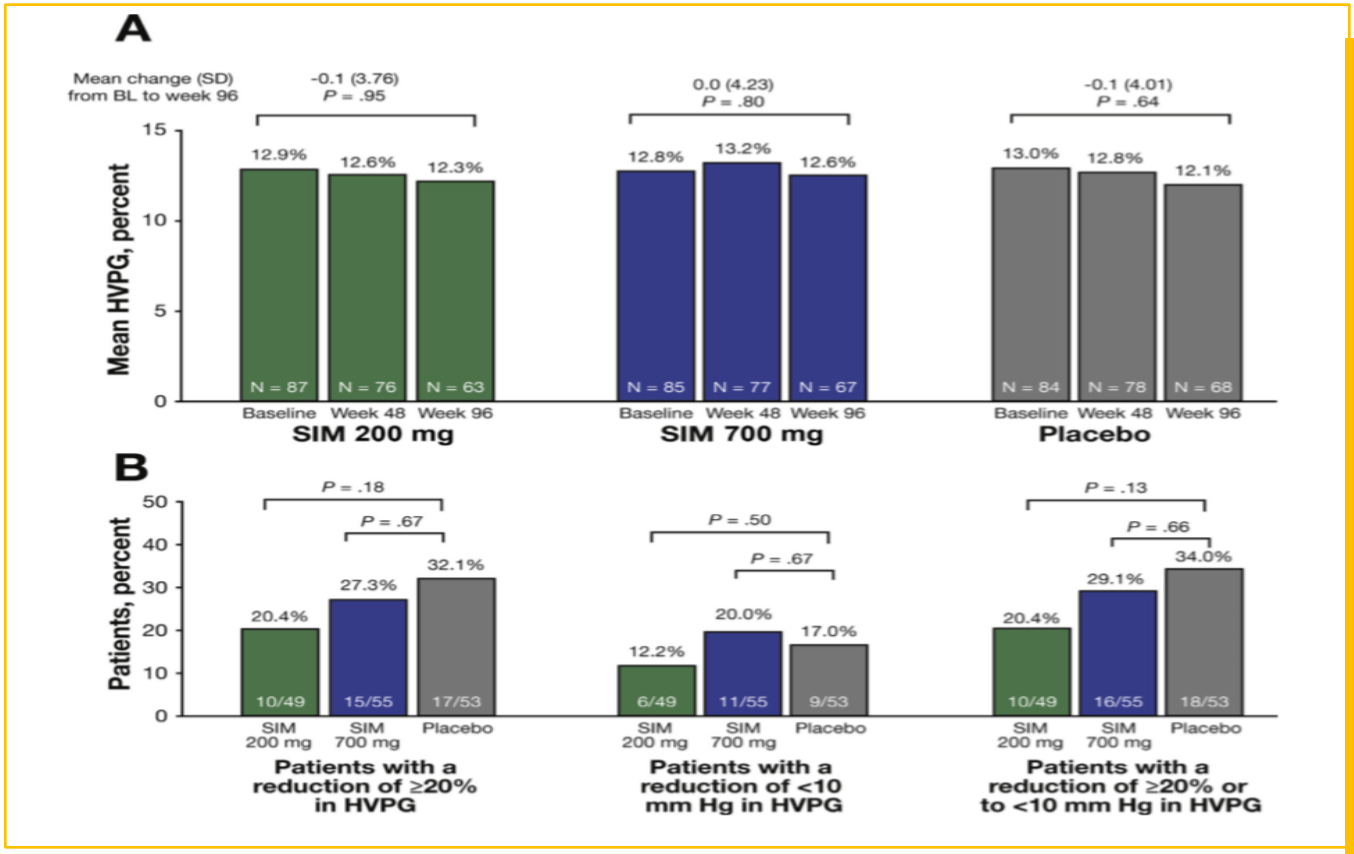
Phase 2b Results: Simtuzumab in NASH Patients with Compensated Cirrhosis



Large, randomized controlled clinical trial (n=258) evaluating two doses of SIM after 48 and 96 weeks of therapy

- **67% with clinically significant portal hypertension and 43% with esophageal varices**
- **Primary endpoint was change in HVPG at week 96**
- **No difference between placebo and treatment groups**
- **32.1% of placebo group had ≥20% reduction in HVPG**

Harrison, et. al., Gastroenterology 2018;155:1140–1153

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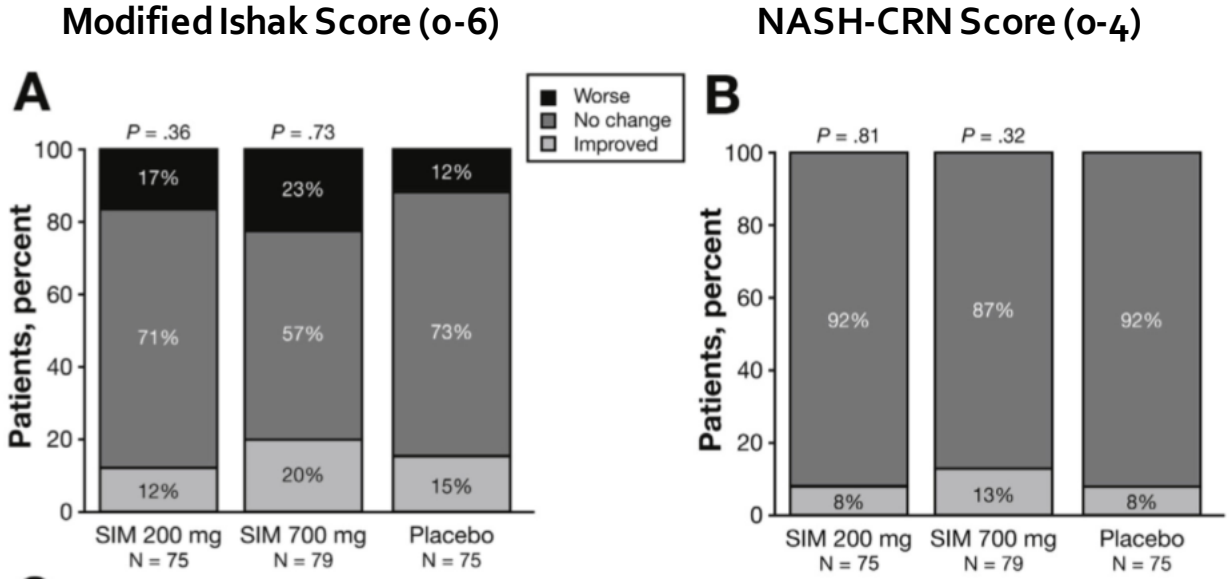
Phase 2b Results: Simtuzumab in NASH Patients with Compensated Cirrhosis



Changes in fibrosis score

- **NASH-CRN score is currently required by regulatory agencies**
- **In placebo patients with median observation of 29 months, 8% had at least a one stage improvement in NASH-CRN score, and there was no difference in SIM groups**

Harrison, et. al., Gastroenterology 2018;155:1140–1153

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Liver-Related Clinical Events in NASH Patients with Compensated Cirrhosis

- **Median follow-up of 30.7 months (IQR 27.6-35)**
- **Liver related clinical events occurred in 18%, 24%, and 15% of SIM200, SIM700, and placebo, respectively; no differences between the groups**

Table 3. Liver-Related Clinical Events in Patients With Compensated Cirrhosis

Event, n (%)	SIM 200 mg (n = 87)	SIM 700 mg (n = 86)	Placebo (n = 85)	Total (n = 258)
Ascites	6 (7)	7 (8)	6 (7)	19 (7)
Encephalopathy	5 (6)	6 (7)	2 (2)	13 (5)
Newly diagnosed varices	2 (2)	1 (1)	1 (1)	4 (2)
Variceal hemorrhage	1 (1)	6 (7)	0	7 (3)
≥2-point increase in CPT score and/or MELD score ≥ 15	2 (2)	1 (1)	3 (4)	6 (2)
Death	0	0	1 (1)	1 (<1)

MELD, Model for End-stage Liver Disease; SIM, simtuzumab; CPT, Child-Pugh-Turcotte.

Harrison, et. al., Gastroenterology 2018;155:1140–1153

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The Critical Cirrhosis Transition: Endpoints for Pre-Cirrhotic NASH

Pre-cirrhotic NASH Endpoints	
Surrogates for Accelerated Approval (agreement with Agencies as part of Phase 3 clinical trials)	**Clinical Outcomes for Full Approval**
Proportion of patients who achieve ≥ 1 stage improvement in fibrosis without worsening of NASH	Reduced time to cirrhosis complications, including the **progression to cirrhosis**
Proportion of patients who achieve NASH resolution without worsening of liver fibrosis	

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The Critical Cirrhosis Transition: Endpoints for NASH Cirrhosis

NASH Cirrhosis Endpoints	
Surrogates for Accelerated Approval (agreement with Agencies as part of Phase 3 clinical trials)	**Clinical Outcomes for Full Approval**
Proportion of patients who achieve ≥ 1 stage improvement in fibrosis without worsening of NASH	Reduced time to cirrhosis complications

The following are potential endpoints as there are no final phase 3 protocols

Reduction in HVPG (endpoints will need to define threshold and degree of reduction in specific populations TBD)	Reduced time to cirrhosis complications
Reduced time to development of esophageal varices in patients with no varices at baseline	Reduced time to cirrhosis complications

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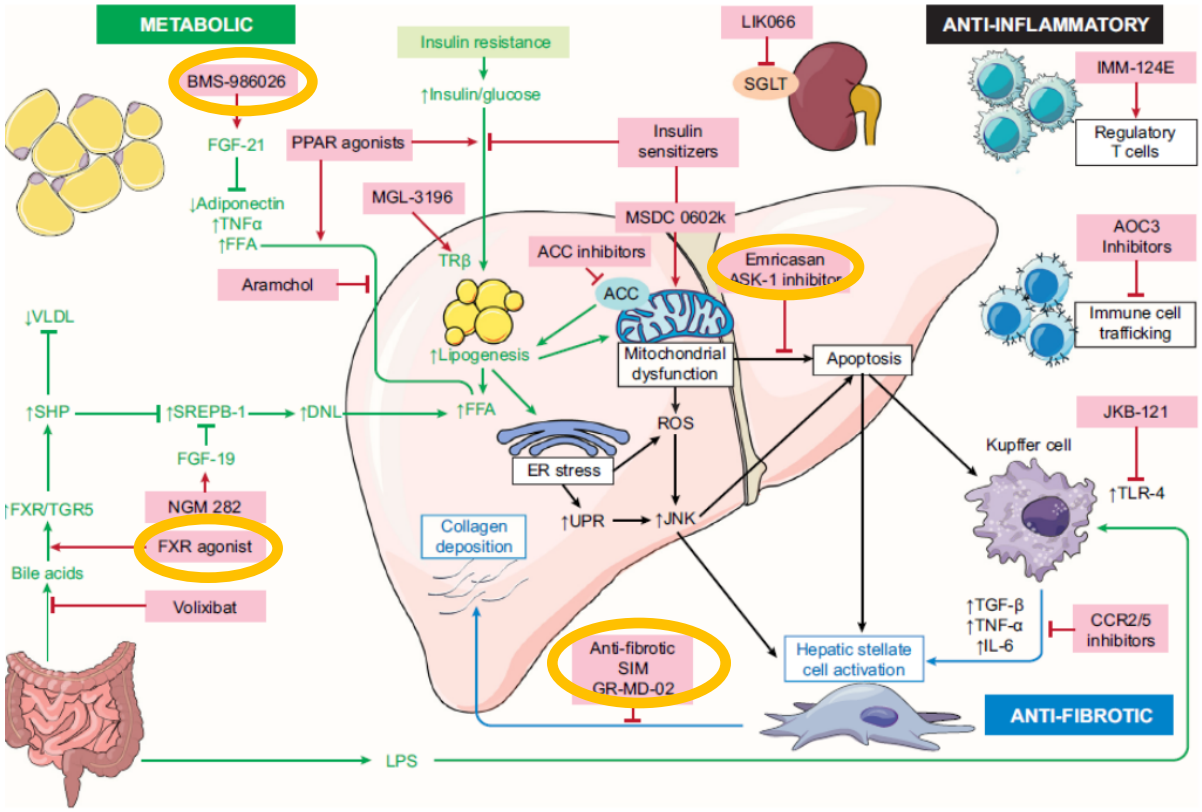
Targets for NASH Therapies



Konerman, et. al., J. Hepatology. 2018

Targets and drugs in current clinical trials for NASH cirrhosis

- **Inhibition of apoptosis pathway**
  - **Emricasan**
  - **Selonsertib**
- **Anti-fibrotic**
  - **Simtuzumab (reported)**
  - **GR-MD-02**
- **Metabolic regulator**
  - **BMS-986026 (FGF-21)**
- **FXR agonist**
  - **Obeticholic Acid**

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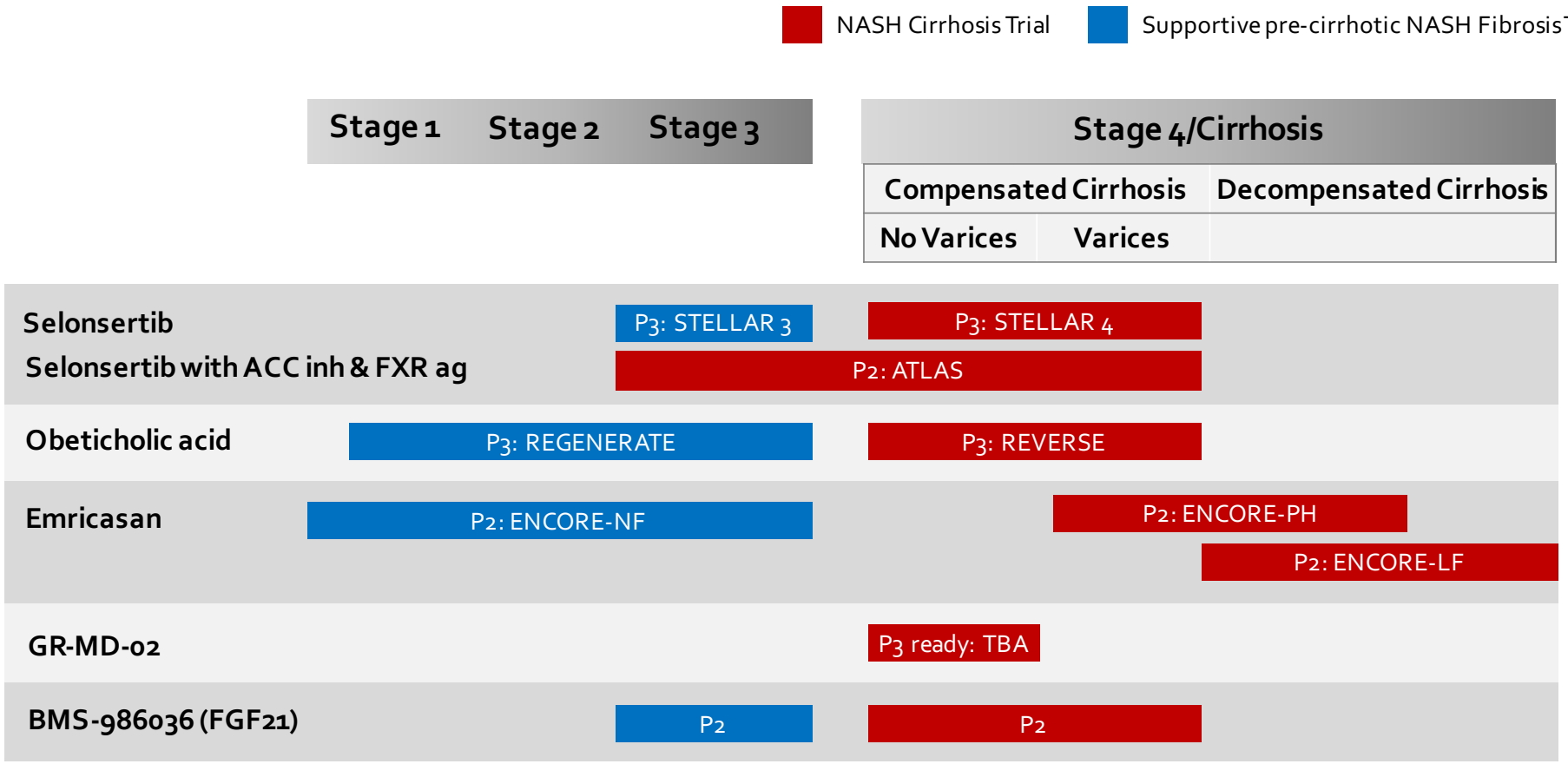
Phase 2/3 Clinical Trials in NASH Cirrhosis

NASH Cirrhosis Trial Supportive pre-cirrhotic NASH Fibrosis Trial

Drug (Company/Partner)	MOA/Route of Administration	Phase	Studies	Next Expected Data (estimate)
Selonsertib (Gilead)	ASK-1 inhib./oral	3 3 2	STELLAR-4: compensated cirrhosis STELLAR-3: NASH with F3 fibrosis ATLAS*: F3 and F4 patients	Q1 2019 Q2 2019 Q1 2020
Obeticholic acid (Intercept)	FXR Agonist/oral	3 3	REVERSE: compensated cirrhosis REGENERATE: NASH with F2/F3 fib	JUL 2020 H1 2019
GR-MD-02 (GALT)	Galectin-3 inhib./iv	3	Compensated cirrhosis w/o varices--Phase 3 start not yet announced	TBA
Emricasan (CNAT/Novartis)	Pan-caspase inhib./oral	2 2 2	ENCORE-PH (severe portal HTN) ENCORE-LF (decompensated cirrhosis) ENCORE-NF (NASH fibrosis)	Q4 2018 H2 2019 H1 2019
BMS-986036 (BMS)	PEG-FGF21/subcut	2	P2b multiple dose; compensated cirrhosis P2b multiple dose; stage 3 fibrosis	JAN 2020 JAN 2020

*** ATLAS study evaluates Selonsertib in combination with GS-0976 (ACC inhibitor) and GS-9674 (FXR agonist)**

NASH Cirrhosis Clinical Trials Mapped to Patient Segment



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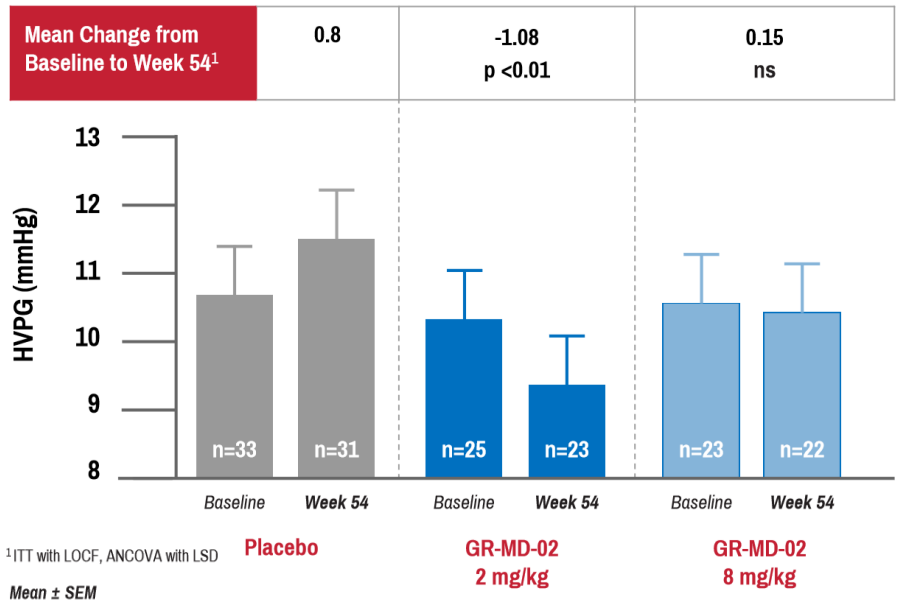
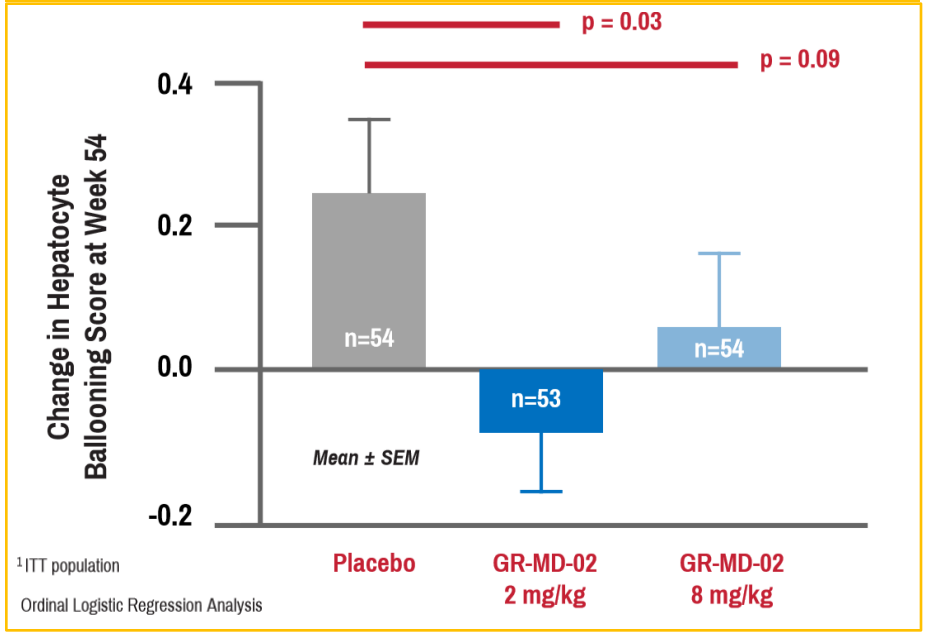
GR-MD-02: Phase 2b NASH Cirrhosis Study Results (NASH-CX)

Compensated Cirrhosis, No Varices (50% Total)[1]



Compensated Cirrhosis (Total Patients[1])



Disclosure: Presenter previously full time employee of GALT, buy currently owns no equity in company. Figures taken from publicly disclosed July 2018 corporate presentation

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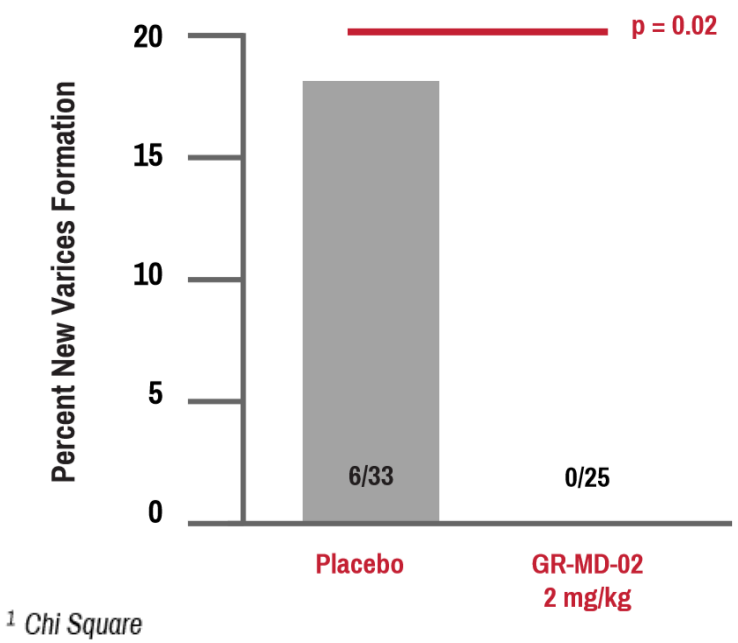
GR-MD-02: Phase 2b NASH Cirrhosis Study Results

Compensated Cirrhosis, No Varices (50% Total)[1]



[1] Chi Square

NASH-CX Study Conclusions

- **First clinical trial to show positive results in compensated cirrhosis without esophageal varices**
  - Clinically meaningful effect in reducing portal pressure in subgroup of patients
  - Improvement in liver cell death
  - Reduction in the development of new varices
- **Drug was safe and well tolerated**
- **Following meeting with FDA in May 2018, determined to be Phase 3-ready**
- **Proceeding with plans for a phase 3 clinical trial program**

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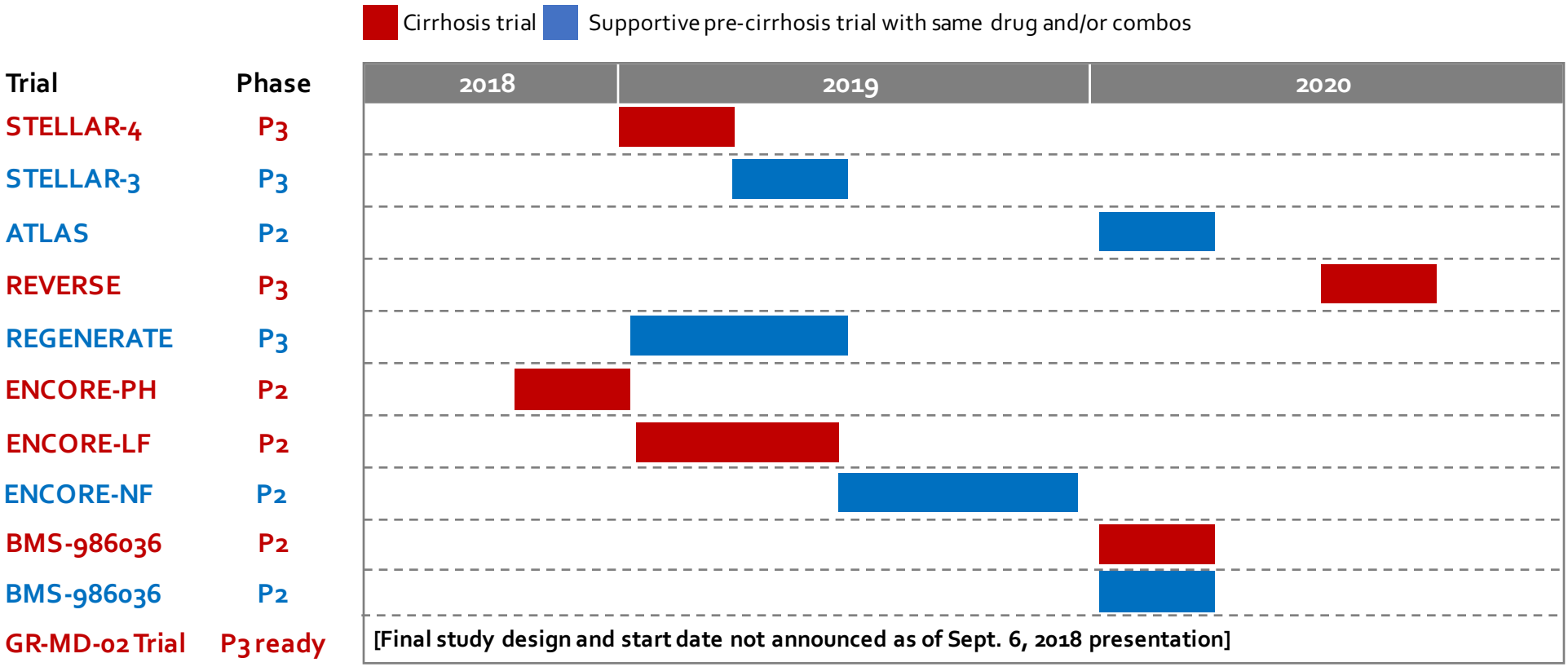
Estimated Data Milestones for NASH Cirrhosis Trials*



* Based on clinicaltrial.gov postings plus company guidance when available; when a specific month was designated, the milestone is indicated over the ensuing one quarter

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Summary Observations Relevant for NASH Cirrhosis Clinical Development

- The natural history in a clinical trial environment of NASH with advanced fibrosis and NASH cirrhosis the is emerging with evaluation of large clinical trials.
- Fibrosis may improve even in the absence of significant weight loss in the context of a clinical trial. Potential factors include dietary changes, reduced alcohol intake, or increased exercise.
- The incidence of cirrhosis complications is relatively low at ~20% over 2.5 years, with the most common being ascites and encephalopathy. Development of new varices and variceal hemorrhage had an incidence of only 2% and 3%, respectively.
- Therapies that target portal hypertension may have utility in reducing complications of cirrhosis
- Extensive data sets will be reported over next 18 months that will substantially clarify natural history and potential for therapeutic intervention in cirrhosis
- Non-invasive and functional testing that effectively predicts the development of cirrhosis and complications of cirrhosis are desperately needed in this field

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Thank You!

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ENCORE-PH: Emricasan in NASH Cirrhosis and Severe Portal Hypertension

Phase 2 Study

# patients	Groups	Inclusion/Exclusion Criteria	Primary Endpoints
▪ 240	▪ EMR 50 mg ▪ EMR 25 mg ▪ EMR 5 mg ▪ Placebo	▪ **Inclusion** › Liver biopsy with NASH cirrhosis › HVPG ≥12 mmHg › Compensated or decompensated with 1 event ▪ **Exclusion** › Severe decompensation › Child-Pugh score ≥10	▪ Mean change in HVPG [Week 24] ▪ In this patient population with HVPG ≥12 mmHg, changes in HVPG may be an acceptable surrogate endpoint

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ENCORE-LF: Emricasan in Decompensated NASH Cirrhosis

Phase 2 Study

# patients	Groups	Inclusion/Exclusion Criteria	Primary Endpoints
▪ 210	▪ EMR 25 mg ▪ EMR 5 mg ▪ Placebo	▪ **Inclusion** › Liver biopsy with NASH cirrhosis › History of variceal hemorrhage or moderate ascites › MELD ≥12 and ≤20 › Albumin ≥12 g/dL › Serum creatine ≤1.5 mg/dL ▪ **Exclusion** › Severe decompensation › Child-Pugh score ≥10	▪ Event-free survival on composite clinical endpoint [final treatment; at least 48 weeks to a max of 120 weeks]

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ENCORE-NF: Emricasan in NASH Fibrosis

Phase 2 Study

# patients	Groups	Inclusion/Exclusion Criteria	Primary Endpoints
▪ 330	▪ EMR 50 mg ▪ EMR 5 mg ▪ Placebo	▪ **Inclusion** › Liver biopsy definitive NASH › NAS ≥4 with 1 in each component › Fibrosis stage 1, 2, or 3 ▪ **Exclusion** › Severe decompensation › Child-Pugh score ≥10	▪ Proportion of patients with ≥ 1 stage improvement in fibrosis without worsening of NASH [week 72]

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BMS-986036 (FGF-21) in Compensated NASH Cirrhosis

Phase 2 Study

# patients	Groups	Inclusion/Exclusion Criteria	Primary Endpoints
▪ 100	▪ 3 dose levels ▪ Placebo	▪ **Inclusion** › Liver biopsy with NASH cirrhosis (Stage 4 by NASH-CRN class) ▪ **Exclusion** › No history of decompensation › No hepatocellular carcinoma	▪ Proportion of patients who achieve a ≥ 1 stage improvement in fibrosis without worsening of NASH [Week 48] ▪ Change in NASH-CRN fibrosis score [Week 48] ▪ Change in NAFLD Activity Score [Week 48]

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BMS-986036 (FGF-21) in NASH with Bridging Fibrosis (stage 3)

Phase 2 Study

# patients	Groups	Inclusion/Exclusion Criteria	Primary Endpoints
▪ 160	▪ 3 dose levels ▪ Placebo	▪ **Inclusion** › Liver biopsy with NASH with bridging fibrosis (Stage 3 by NASH CRN classification) › NASH with a score of at least 1 for steatosis, lobular inflammation, and ballooning ▪ **Exclusion** › No history of decompensation › No hepatocellular carcinoma	▪ Proportion of patients who achieve a ≥ 1 stage improvement in fibrosis without worsening of NASH [week 24] ▪ Proportion of patients who achieve NASH improvement with no worsening of fibrosis [week 24] ▪ Change in NAFLD Activity Score [Week 24]

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