A multicenter, randomized, double-blind, placebo-controlled trial of Galectin-3 inhibitor (GR-MD-02) for one year in patients with NASH cirrhosis and portal hypertension

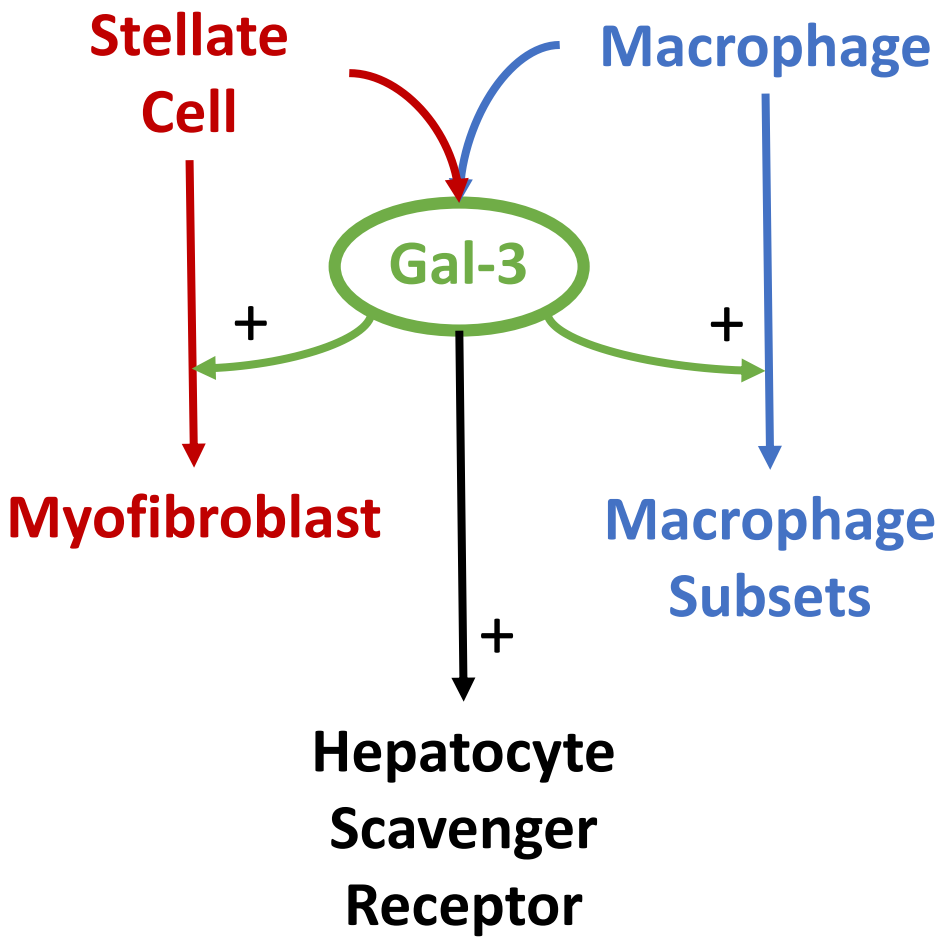
The NASH-CX Trial

[1]Naga Chalasani, [2]Guadalupe Garcia-Tsao, [3]Zachary Goodman, [4]Eric Lawitz, [5]Manal Abdelmalek, [6]Mary Rinella, [7]Michael Ryan, [8]Mazen Noureddin, [9]Christopher Jue, [1]Maxmillan Pyko, [10]Adam Allgood, [10]Harold Shlevin, [10]Rex Horton, [10]Eliezer Zomer, [10]Peter G. Traber, [11]Rohit Loomba, [12]Brent Neuschwander-Tetri, [13]Arun Sanyal, [14]Stephen A Harrison

[1]Indiana University, Indianapolis, IN, [2]Yale University, New Haven, CT, [3]INOVA Fairfax Hospital, Fairfax, VA, [4]Texas Liver Institute, San Antonio, TX, [5]Duke University, Durham, NC, [6]Northwestern University, Chicago, IL, [7]Digestive and Liver Disease Specialists, Norfolk, VA, [8]Cedars Sinai Medical Center, Los Angeles, CA, [9]Digestive Health Specialists, Winston-Salem, NC, [10]Galectin Therapeutics, Norcross, GA, [11]UCSD, San Diego, CA, [12]St. Louis University, St. Louis, MO, [13]VCU, Richmond, VA, [14]Pinnacle Clinical Research, San Antonio, TX

Rationale for Galectin-3 Inhibition in NASH

- Gal-3 is a lectin protein that binds to galactose residues on glycoproteins and is increased in NASH and liver fibrosis/cirrhosis
- Gal-3 null mice are resistant to NASH and fibrosis
- Gal-3 involved in multiple pathophysiologic processes in NASH and liver fibrosis
- GR-MD-02 is a complex carbohydrate drug that inhibits gal-3 and improves pathology of NASH and reverses fibrosis/cirrhosis in animal models [1,2]
- Safe and well tolerated in normal and NASH patients with advanced fibrosis in Phase 1 studies



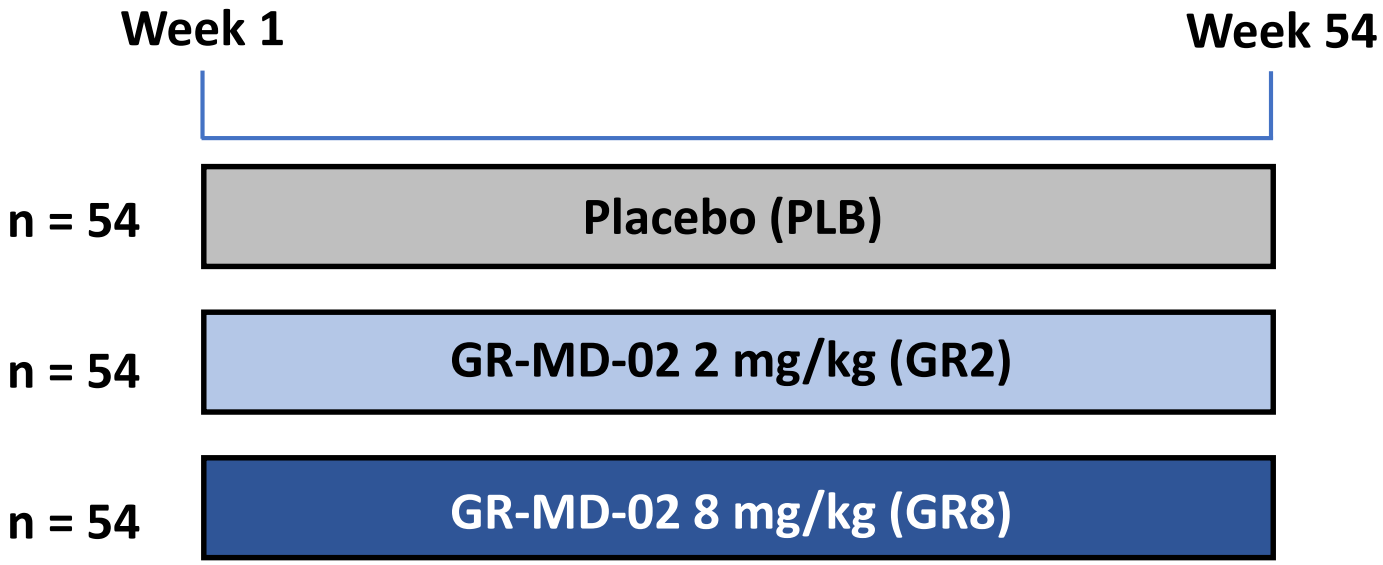
[1] Traber PG and Zomer E.PLOS ONE 2013;8:e83481

[2] Traber PG, Chou H, Zomer E, Hong F, Klyosov A Fiel M-I, Friedman, SL. PLOS ONE 2013;8:e75361.

NASH-CX Clinical Trial Design

AIM: Evaluate Safety and Efficacy of GR-MD-02 in Compensated NASH Cirrhosis

Major Inclusion Criteria		
	NASH cirrhosis (biopsy) HVPG ≥ 6 mmHg	No decompensating event No or small varices



Every other week intravenous infusion X 26

Study Endpoints & Assessment Methods

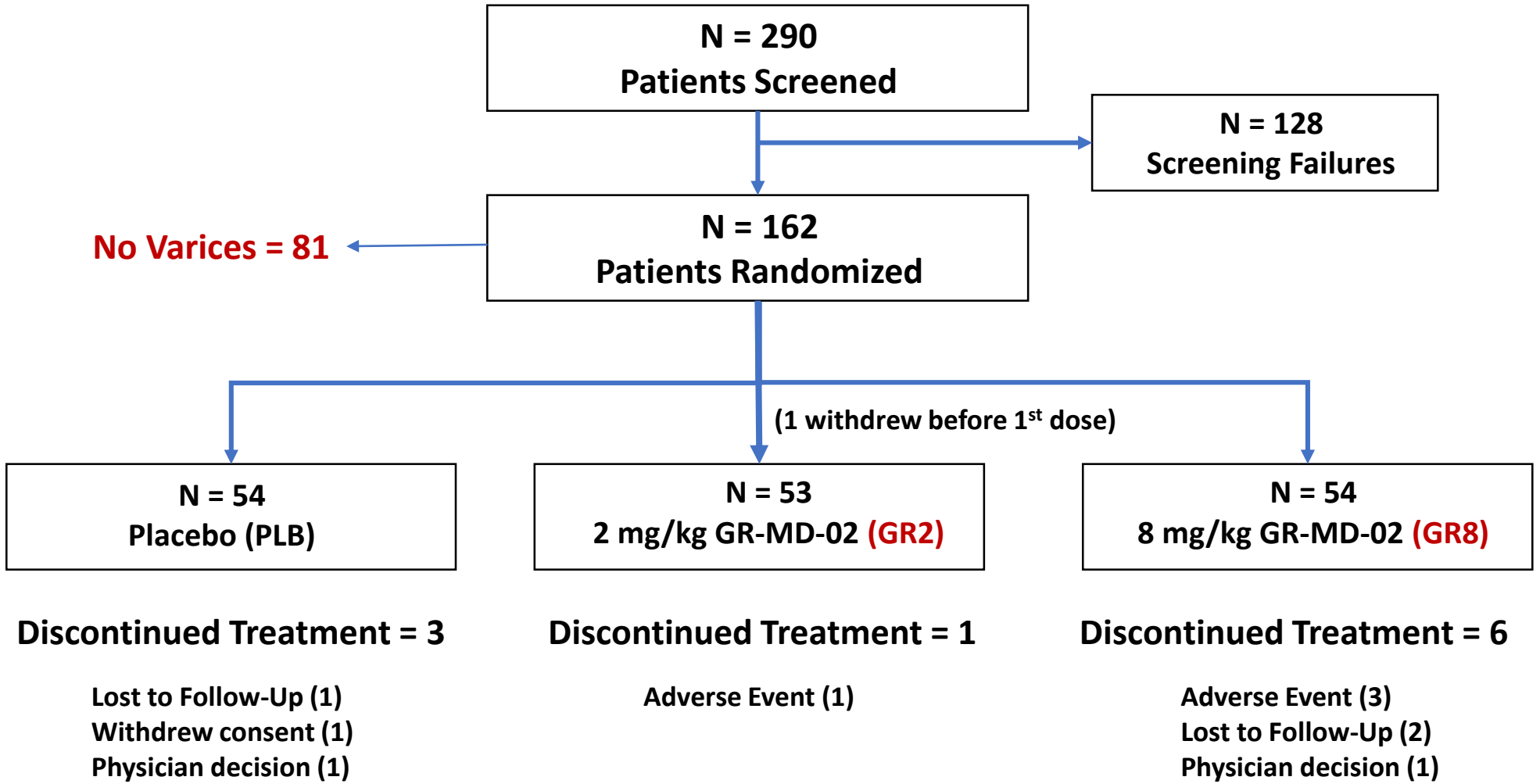
➢ Primary Endpoint

- **Change in Hepatic Venous Pressure Gradient (HVPG)**
  - Baseline and Week 54
  - Standardized Procedure and Central Blinded Reading

➢ Secondary Endpoints

- **Change in Liver Histology**
  - NAFLD Activity Score and Fibrosis Staging
  - Quantitative Morphometry for Collagen
  - Baseline and week 54
  - Central Blinded Reading
- **Endoscopy to Evaluate for Varices**
- **Complications of Cirrhosis**

Study Disposition (36 US Sites)



Study Demographics & Baseline Assessments

	Total (n=162)	Placebo (n=54)	GR2 (n=54)	GR8 (n=54)
Age, years; median (IQR)	59 (52, 65)	59 (53, 64)	60 (53, 65)	58 (51, 63)
Female, n (%)	113 (70)	36 (67)	34 (63)	43 (79)
Non-Hispanic White, n (%)	132 (81)	46 (85)	46 (85)	40 (74)
BMI, kg/m^2; median (IQR)	34 (31, 39)	34 (30, 38)	36 (31, 41)	35 (31, 38)
Diabetes, n (%)	100 (62)	32 (59)	32 (59)	36 (67)
AST (U/L) mean ± SD	49.8 ± 33.8	51.9 ± 48.2	48.3 ± 23.0	49.3 ± 24.8
ALT (U/L) mean ± SD	47.1 ± 34.1	48.1 ± 38.1	42.4 ± 21.0	50.9 ± 40.1
ELF Score mean ± SD	10.7 ± 1.2	10.8 ± 1.1	10.7 ± 1.2	10.7 ± 1.2
NAFLD Activity Score	4.2 ± 1.6	4.2 ± 1.5	4.3 ±1.3	4.2 ± 1.6
Ishak Stage (5/6)	48/123	13/41	20/43	15/39
Collagen (%) mean ± SD	10.5 ± 6.1	10.8 ±6.5	9.7 ± 5.9	11.0 ± 6.1

IQR=interquartile range; BMI=body mass index; AST=aspartate transaminase; ALT=alanine transaminase; ELF=enhanced liver fibrosis; NAFLD=non-alcoholic fatty liver disease

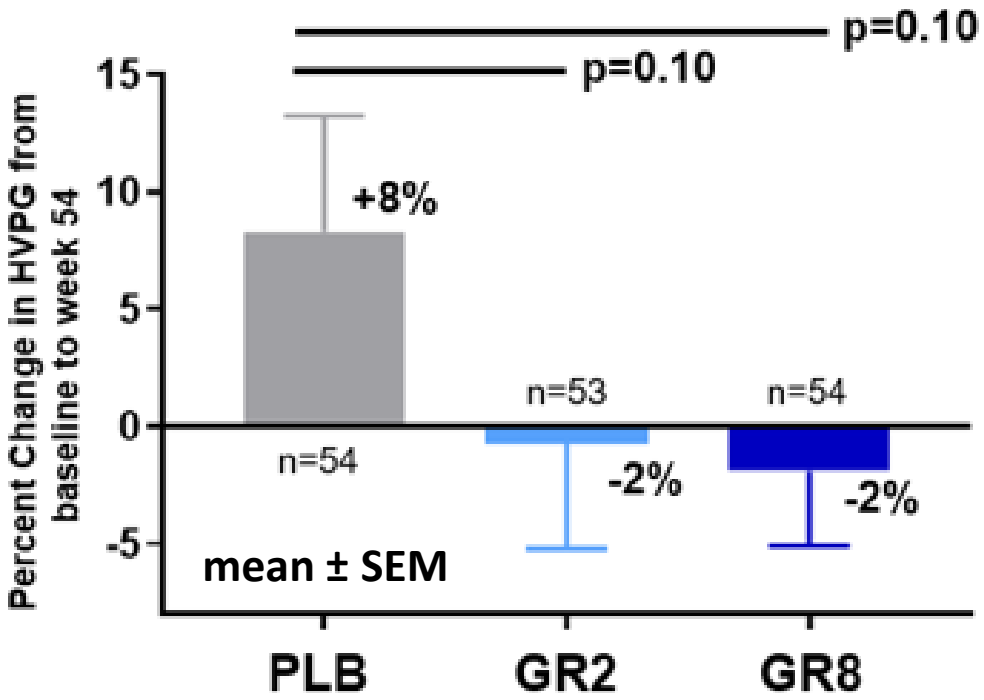
Baseline HVPG (mmHg) in Patient Groups

	Total Mean ± SD (n)	Placebo Mean ± SD (n)	GR2 Mean ± SD (n)	GR8 Mean ± SD (n)
Full Analysis Set	12.2 ± 4.2 (162)	11.6 ± 4.0 (54)	12.4 ± 4.3 (54)	12.7 ± 4.2 (54)
CSPH Sub-group	14.3 ± 3.4 (108)	14 ± 3.1 (33)	14.2 ± 3.9 (37)	14.8 ± 3.1 (38)
MPH Sub-Group	7.9 ± 1.2 (53)	7.8 ± 1.3 (21)	8.2 ± 1.0 (16)	7.8 ± 1.3 (16)
No Varices Sub-Group	10.6 ± 3.5 (81)	10.8 ± 3.8 (33)	10.3 ± 2.9 (25)	10.7 ± 3.8 (23)
With Varices Sub-Group	13.9 ± 4.2 (80)	12.9 ± 4.1 (21)	14.2 ± 4.6 (28)	14.2 ± 3.9 (31)

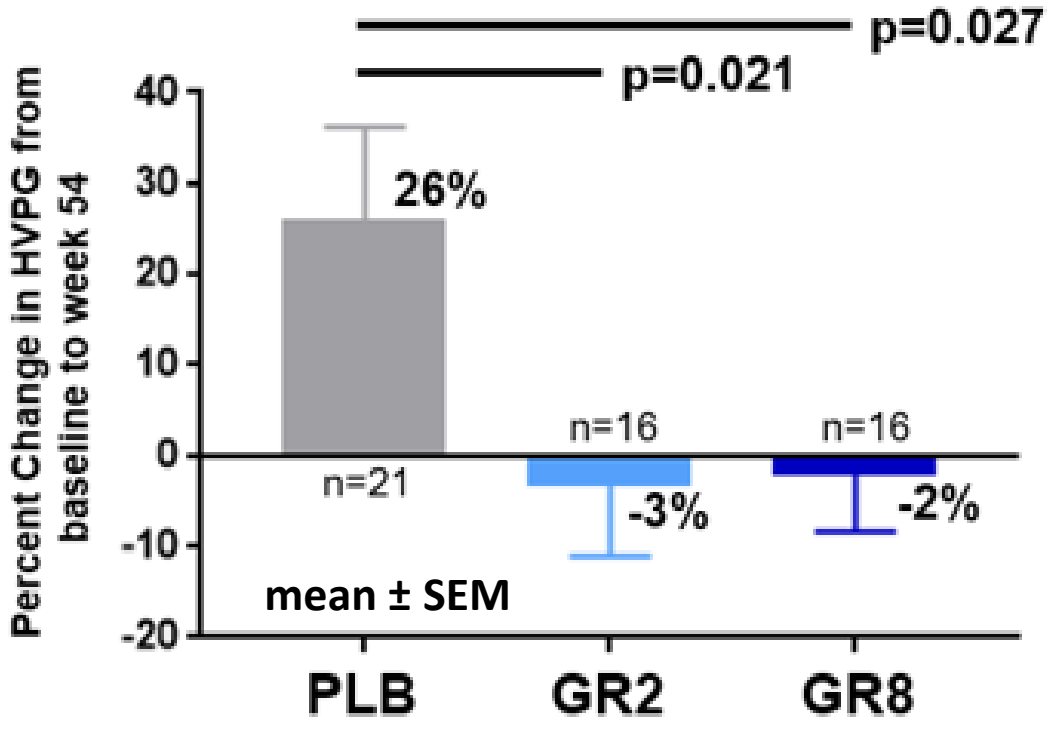
There were no statistical differences between the three treatment groups for any of the measures.
CSPH=clinically significant portal hypertension (≥ 10 mm Hg).
MPH=mild portal hypertension (≥ 6 and < 10 mm Hg).

HVPG Primary Endpoint (Pre-Specified Analyses)

Total Patient Population



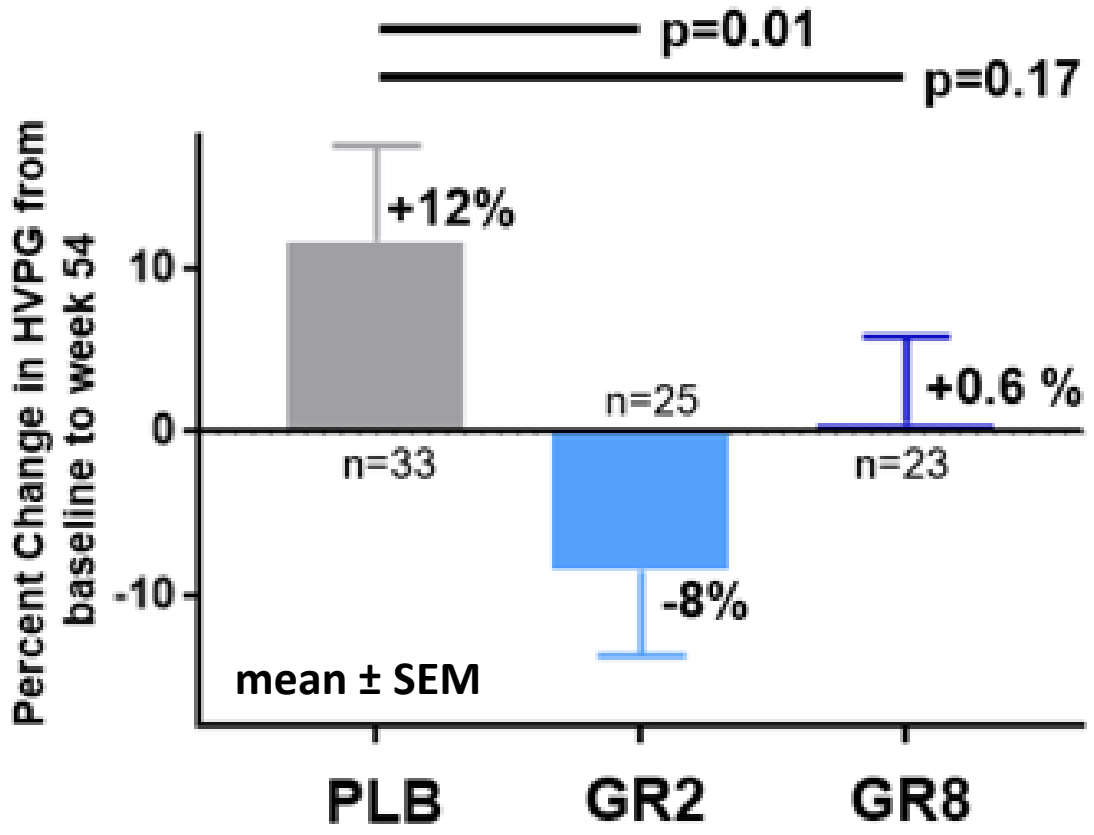
Mild Portal Hypertension



ITT with LOCF (last observation carried forward); ANOVA with LSD (least squared difference)

No Esophageal Varices at Baseline (Post Hoc Analysis)

50% of patients (81) did not have varices at baseline

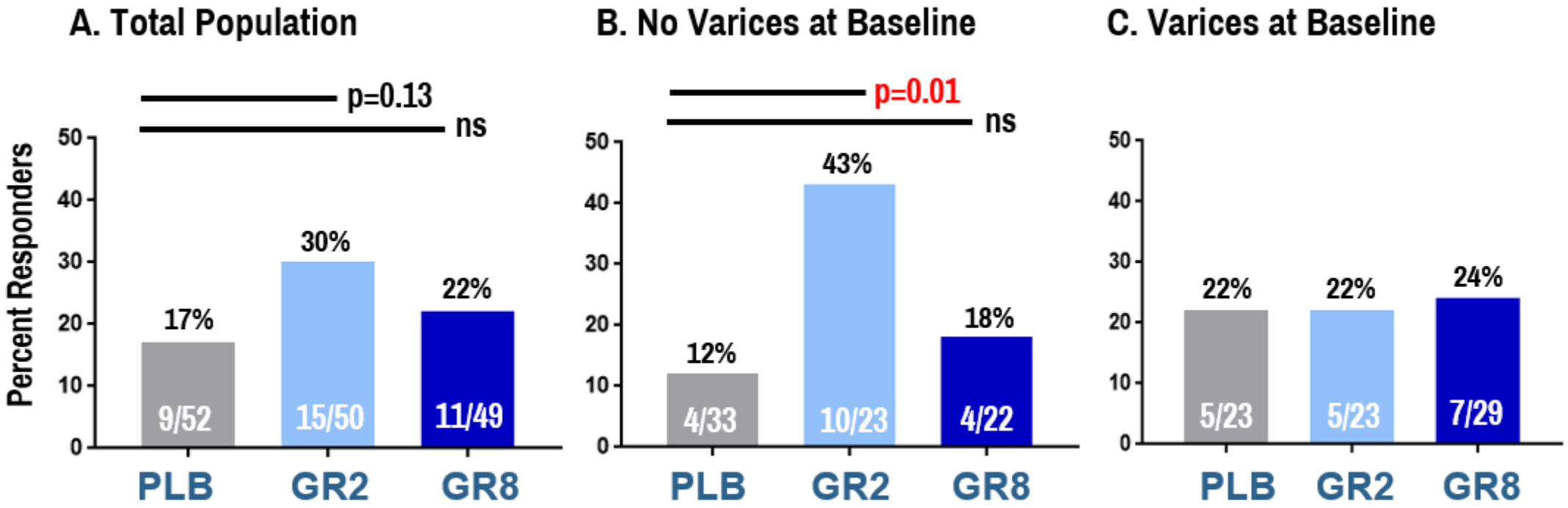


ITT with LOCF; ANOVA with LSD

Responder Analysis (Post Hoc Analysis)

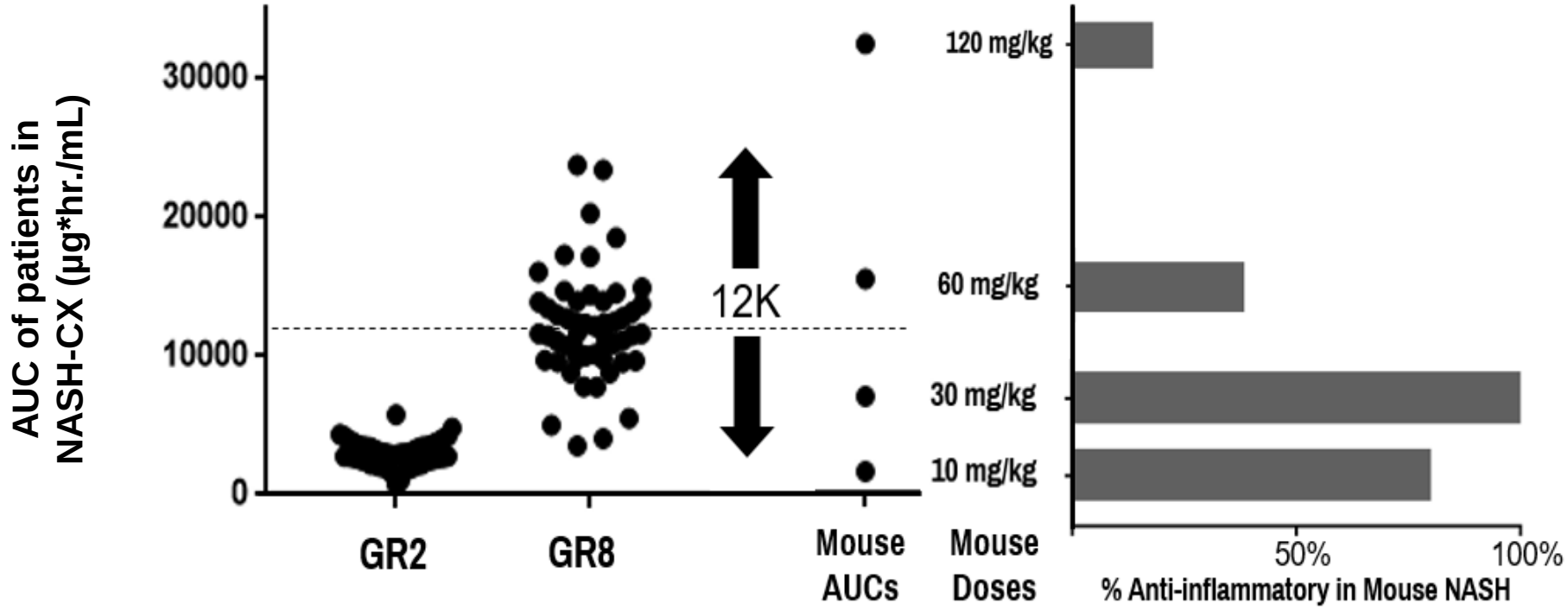
Percentage of Patients Who Had a Clinically Relevant Reduction in HVPG With:

- **≥ 2 mmHg Decrease From Baseline AND**
- **≥ 20% Decrease From Baseline**



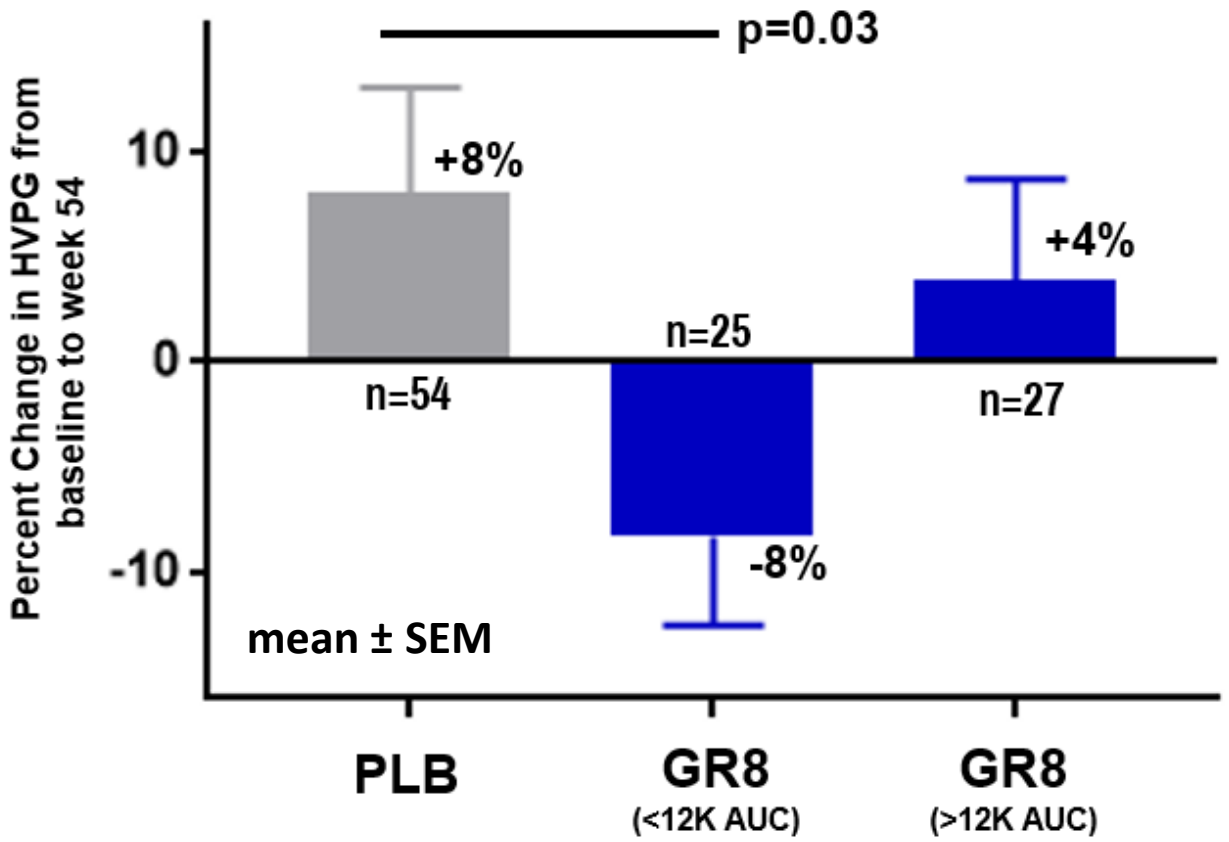
Chi Square Analysis

PK-PD Correlation Between Human and Mouse Data



[1]Traber, P.G. and E. Zomer, *Therapy of experimental NASH and fibrosis with galectin inhibitors.* PLoS. One, 2013. 8(12): p. e83481.

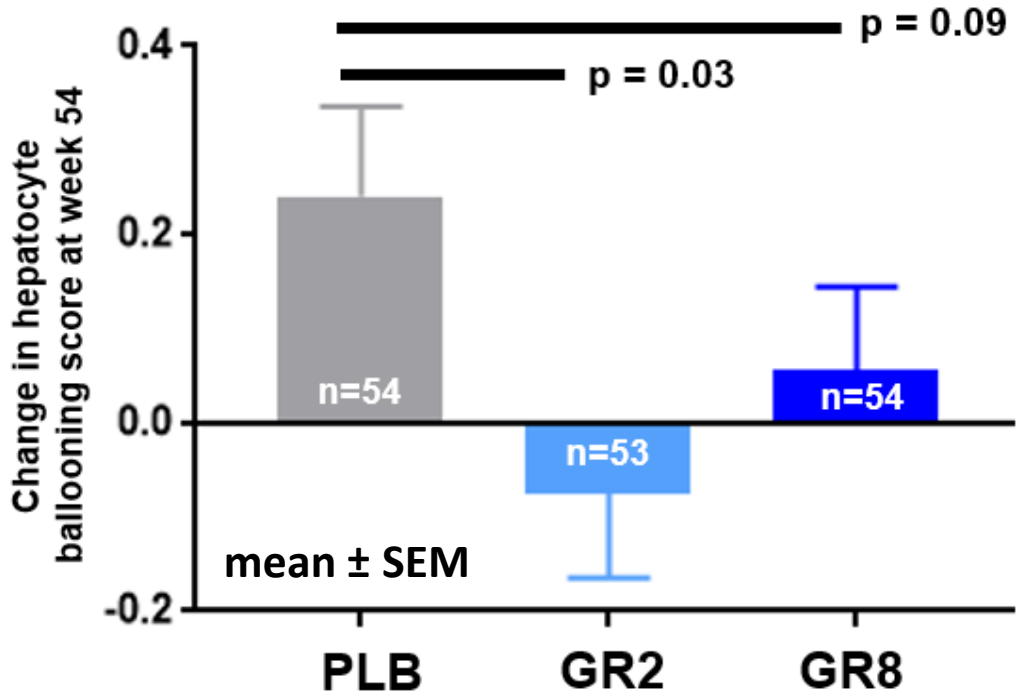
Change in HVPG Using PK Range Groups for GR8



ITT; ANOVA with LSD; AUC=area under concentration curve (µg*hr./mL)

Changes in Liver Histology in Total Patient Population

- Trend towards improvement in NAS that did not reach significance
- No differences in steatosis across the treatment groups
- Statistically significant difference between GR2 and placebo for inflammation scores in the patients without baseline varices
- There was no effect on fibrosis staging or percent collagen on morphometry
- Statistically significant improvement in hepatocyte ballooning in GR2 group and trend in GR8 group



ITT Analysis Set; Ordinal logistic regression analysis

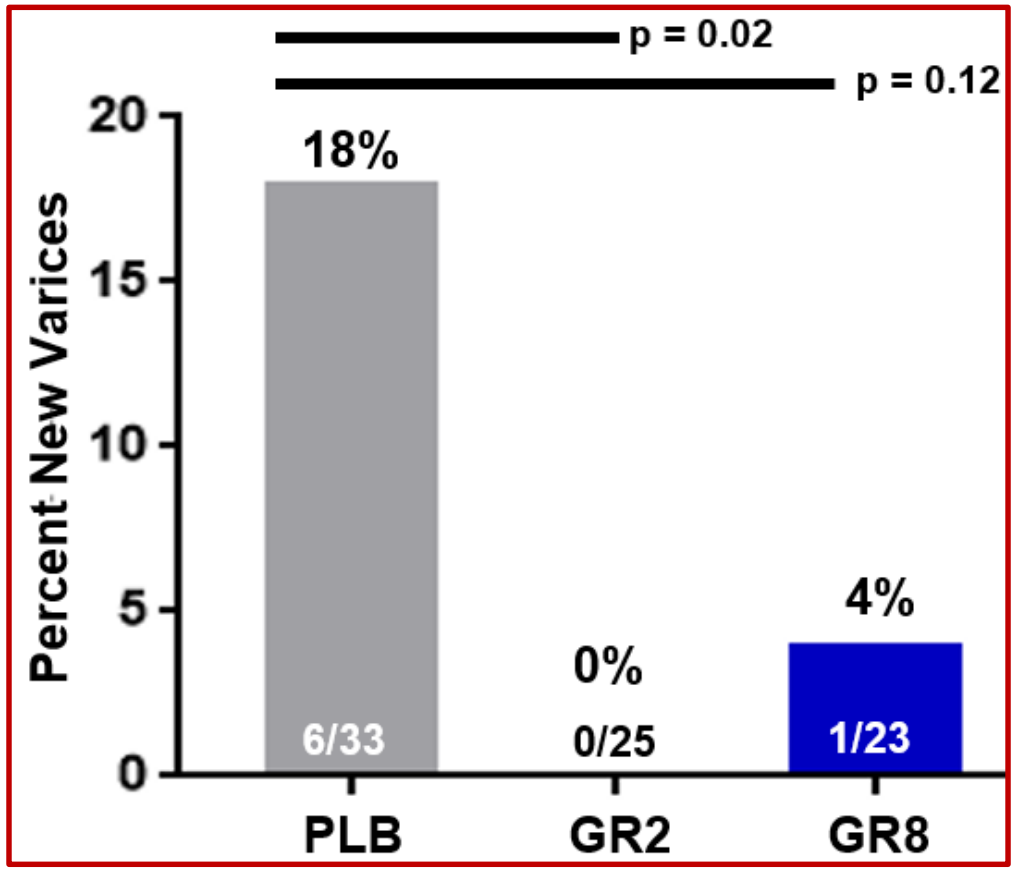
Correlation of Liver Biopsy Findings in HVPG Responders

Total Patient Population

	GR2[1]	GR8[1]
Hepatocyte Ballooning	**0.04**	**0.05**
NAFLD Activity Score	0.19	0.28
Ishak Stage	0.20	0.59

[1]p value compared to placebo
Ordinal logistic regression analysis was used to compare groups. ITT analysis set.

Fewer Patients in GR Groups Developed New Varices



Chi Square Analysis

Development of Cirrhosis Complications[1]

	Total	PLB	GR2	GR8
FAS Population	n=161	n=54	n=53	n=54
• Complications – n(%)	21 (13)	9 (17)	5 (9)	7 (13)
No-Varices Population	n=81	n=33	n=25	n=23
• Complications – n(%)	12 (15)	7 (21)	3 (12)	2 (9)
MPH Population	n=53	n=21	n=16	n=16
• Complications – n(%)	4 (8)	3 (14)	1 (6)	0

[1] Development of new varices
Variceal hemorrhage
Clinically significant ascites
Overt hepatic encephalopathy
↑ CTP score ≥ 2
↑ MELD to ≥ 15
Liver transplantation or death

Adverse Events

	Total (n=161)	PLB (n=54)	GR2 (n=53)	GR8 (n=54)
Treatment Emergent (TE) AEs	1323	431	509	383
Patients with at least ≥ grade 3 AE (%)	33 (20.5)	11 (20.4)	11 (20.8)	11 (20.4)
Patients with at least 1 TE SAE[1] (total)	25 (34)	8 (10)	5 (10)	12 (14)
Study drug discontinued due to AE	3	0	0	3[2]
Death	1	0	1[3]	0

[1] Two treatment emergent SAEs were rated by PI as possibly related to study drug (transient ischemic attack and worsening of hyponatremia, both GR8) but were rated by sponsor as unrelated; All other SAEs were unrelated to study drug

[2] *Probably related to drug*: spasmodic cough (1); *Unrelated to study drug:* esophageal variceal bleeding (2).

[3] Pulmonary embolism following hernia repair surgery, judged to be unrelated to study drug

Conclusions

- Change in HVPG associated with GR treatment was not significant in total patient population, but statistically significant in the pre-specified group of mild portal hypertension
- In patients without varices at baseline, there was a statistically significant difference in the GR2 group in the change in HVPG, percentage of responders, and development of new varices
- GR treatment improved hepatocyte ballooning in the total, which correlated with an improvement in HVPG
- Less pronounced effects of GR8 may be explained by its variable pharmacokinetics
- GR 2 and GR 8 treatment was well-tolerated with no safety signals
- These results warrant further trials with GR-MD-02 in compensated NASH cirrhotic patients without esophageal varices or those with mild portal hypertension

Acknowledgements

We extend our thanks to the patients, their families and all participating investigators

Indiana University School of Medicine-Dr. Chalasani
The Texas Liver Institute-Dr. Lawitz
Duke University Medical Center-Dr. Abdelmalek
Feinberg School of Medicine - Northwestern University-Dr. Rinella
Pinnacle Clinical Research, PLLC-Dr. Harrison
Digestive and Liver Disease Specialists-Dr. Ryan
Cedars Sinai Medical Center-Dr. Noureddin
Digestive Health Specialists, PA-Dr. Jue
Medical University of South Carolina-Dr. Rockey
Thomas Jefferson University-Dr. Halegoua-De Marzio
Texas Clinical Research Institute LLC-Dr. Ghalib
Virginia Commonwealth University-Dr. Sanyal
University of Mississippi Medical Center-Dr. Borg
Bon Secours Richmond Health System-Dr. Shiffman
University of Colorado Denver-Dr. Wieland
Columbia University Medical Center-Dr. Wattacheril
University of Michigan-Dr. Conjeevaram
Mcguire Veterans Affairs Medical Center-Dr. Fuchs
Baylor College of Medicine-Dr. Vierling
Piedmont Hospital-Dr. Rubin
Mary Immaculate Hospital-Dr. Shiffman
Saint Louis University-Dr. Tetri
Mercy Medical Center-Dr. Thuluvath
Swedish Medical Center-Dr. Kowdley
UH Cleveland Medical Center-Dr. Gholam
International Medical Investigations Center-Dr. Rodriguez
Intermountain Medical Center-Dr. Charlton
Tulane University Health Sciences Center-Dr. Balart
Vanderbilt University Medical Center-Dr. Scanga
Walter Reed National Military Medical Center-Dr. Torres
Tampa General Medical Group-Dr. Kemmer
University of California San Diego Medical Center-Dr. Loomba
Beth Israel Deaconess Medical Center-Dr. Lai
University Gastroenterology-Dr. Sepe
Minnesota Gastroenterology PA-Dr. Zogg
Brooke Army Medical Center-Dr. Paredes

HVPG

Yale University School of Medicine-Dr. Garcia-Tsao

Liver Biopsy

Inova Fairfax Hospital-Dr. Goodman

This study was funded by Galectin Therapeutics, Inc.