Clinical Trials & Endpoints in NASH Cirrhosis

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Chronic Liver Disease, Cirrhosis and its Progression

- **Chronic Liver Disease**
  - NASH
  - Viral Hepatitis
  - Alcohol
  - Other

  **↑ Liver Fibrosis**

  **Compensated Cirrhosis**
  - Variceal Bleeding
  - Ascites
  - Encephalopathy
  - Jaundice/Liver Failure

  ** Decompensated Cirrhosis**
  - Hepatocellular Carcinoma
Survival Between Compensated and Decompensated Cirrhosis

D’Aminco et. Al., J Hepatol 2006;44:217 (Graphic borrowed from Dr. Guadalupe Garcia-Tso)
Portal Hypertension is the Main Driver of Decompensation

**Compensated Cirrhosis**

- **Stage 1**: NO
- **Stage 2**: 7% → YES

**Decompensated Cirrhosis**

- **Stage 3**: YES/NO
- **Stage 4**: YES

**Ascites**

- **Stage 1**: NO
- **Stage 2**: 4.4% → NO
- **Stage 3**: YES
- **Stage 4**: YES/NO

**Bleed**

- **Stage 1**: NO
- **Stage 2**: NO
- **Stage 3**: NO
- **Stage 4**: YES

**Mortality**

- **Stage 1**: 1%
- **Stage 2**: 3%
- **Stage 3**: 20%
- **Stage 4**: 57%

D’Aminco et. Al., J Hepatol 2006;44:217
Portal Hypertension is Initiated by Increased Intrahepatic Resistance
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”
Cirrhosis Complications Center Around Increased Portal Vein Blood Pressure

- Encephalopathy
- Shunting
- Hepatic Insufficiency

**Portal Hypertension**

- Increased Resistance
- Increased Flow
- Ascites

- Effective Hypovolemia
- Increased Cardiac Output
- Na/H2O Retention
- Splanchnic vasodilatation
- Neurohormonal Activation

- Varices
Critical Importance of Esophageal Varices in Cirrhosis

An important goal of treatment of patients with compensated cirrhosis without esophageal varices is to prevent progression to varices and complications.
In Compensated HCV Cirrhosis, the Presence of Varices is Associated with Greater Probabilities of Decompensation and Death

Bruno et. al., Am J Gastro 2009;104:1147 (Graphic borrowed from Dr. Guadalupe Garcia-Tso)
In Compensated HCV Cirrhosis, the Presence of Varices Prior to HCV Treatment Determines Decompensation Post-SVR

DiMarco et. al., Gastroenterology 2016;151:131 (Graphic borrowed from Dr. Guadalupe Garcia-Tso)
Targeting NASH Cirrhosis

Estimated US Prevalence
- 80 - 100M
- 24 - 30M

NASH: Cell Death, Inflammation, Fibrosis

Compensated Cirrhosis
- Stage 1: No Varices
- Stage 2: Varices Develop

Decompensated Cirrhosis
- Stage 3 and 4: Bleeding, Ascites, Encephalopathy

Portal Pressure (mmHg)
- ≥6
- >10
- >12

1 Garcia-Tsao, G., Friedman, S., Iredale, J., Prinzani, M. Hepatology. 2010;51:14451449
## Potential Clinical Trial Endpoints in NASH Cirrhosis

| **Patient Outcomes** | **Feels, functions, and survival**  
Decompensation events: bleeding varices, ascites, hepatic encephalopathy, transplant, death  
HCC; Patient reported quality of life (?) |
|----------------------|----------------------------------------------------------------------------------|
| **Portal Pressure**   | **Hepatic Venous Pressure Gradient**  
Crossing thresholds  
Absolute or percent change  
Responder definitions |
| **Liver Biopsy**      | Reversal of cirrhosis (NASH-CRN stage 4 to a lower stage)  
Reduction in the percent of collagen (morphometry) |
| **Imaging/Structure** | Measures of liver stiffness: US (e.g. FibroScan, ARFI); MRE  
Multiparametric MRI (e.g. Perspectum LiverMultiScan); PDFF |
| **Composite Scores**  | MELD Score  
Child-Turcotte-Pugh Score; ELF and others |
| **Liver Function**    | Metabolism: $^{13}$C methacetin breath test (Exalenz)  
Bile acid handling: HepQuant Shunt/Stat |

**FDA Agreement**  
**FDA: May Be Surrogate Endpoint**
# Liver Function Should be Area of Future Focus, as in Other Organ Failure

## Patient Outcomes

**Feels, functions, and survival**
- Decompensation events: bleeding varices, ascites, hepatic encephalopathy, transplant, death
- HCC; Patient reported quality of life (?)

## Liver Function

Metabolism: $^{13}$C methacetin breath test
- Bile acid handling: HepQuant Shunt/Stat

## Portal Pressure

**Hepatic Venous Pressure Gradient**
- Crossing thresholds
- Absolute or percent change
- Responder definitions

## Liver Biopsy

- Reversal of cirrhosis (NASH-CRN stage 4 to a lower stage)
- Reduction in the percent of collagen (morphometry)

## Imaging/Structure

- Measures of liver stiffness: US; MRE
- Multiparametric MR; PDFF

## Composite Scores

- MELD Score
- Child-Turcotte-Pugh Score; ELF and others
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.
NASH-CX Clinical Trial Design

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

**Major Inclusion Criteria**

| NASH cirrhosis (biopsy) | No decompensating event
<table>
<thead>
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<tbody>
<tr>
<td>HVPG ≥ 6 mmHg</td>
<td>No or small varices</td>
</tr>
</tbody>
</table>

**Week 1**

- n = 54
  - Placebo (PLB)

**Week 54**

- n = 54
  - GR-MD-02 2 mg/kg (GR2)
- n = 54
  - GR-MD-02 8 mg/kg (GR8)

*Every other week intravenous infusion X 26*
Study Endpoints & Assessment Methods

- **Primary Endpoint (baseline and week 54)**
  - Change in Hepatic Venous Pressure Gradient (HVPG)
    - Standardized Procedure and Central Blinded Reading

- **Secondary Endpoints (baseline and week 54)**
  - Change in Liver Histology
    - NAFLD Activity Score and Fibrosis Staging
    - Quantitative Morphometry for Collagen
    - Central Blinded Reading
  - Endoscopy to Evaluate for Varices
  - $^{13}$C Methacetin Breath Test (Exalenz)
  - FibroScan
  - Complications of Cirrhosis
Study Disposition (36 US Sites)

N = 290 Patients Screened

N = 128 Screening Failures

N = 162 Patients Randomized

No Varices = 81

N = 54 Placebo (PLB)
- Discontinued Treatment = 3
  - Lost to Follow-Up (1)
  - Withdrew consent (1)
  - Physician decision (1)

N = 53 2 mg/kg GR-MD-02 (GR2)
- Discontinued Treatment = 1
  - Adverse Event (1)

N = 54 8 mg/kg GR-MD-02 (GR8)
- Discontinued Treatment = 6
  - Adverse Event (3)
  - Lost to Follow-Up (2)
  - Physician decision (1)
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

mean ± SEM
Responder Analysis (Post Hoc Analysis)

Percentage of Patients Who Had a Clinically Relevant Reduction in HVPG With:
- \( \geq 2 \text{ mmHg Decrease From Baseline AND} \)
- \( \geq 20\% \text{ Decrease From Baseline} \)

A. Total Population

<table>
<thead>
<tr>
<th>Group</th>
<th>Percent Responders</th>
<th>p-value</th>
<th>ns</th>
</tr>
</thead>
<tbody>
<tr>
<td>PLB</td>
<td>17%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>GR2</td>
<td>30%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>GR8</td>
<td>22%</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

B. No Varices at Baseline

<table>
<thead>
<tr>
<th>Group</th>
<th>Percent Responders</th>
<th>p-value</th>
<th>ns</th>
</tr>
</thead>
<tbody>
<tr>
<td>PLB</td>
<td>12%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>GR2</td>
<td>43%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>GR8</td>
<td>18%</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

C. Varices at Baseline

| Group | Percent Responders |  
|-------|-------------------|---|
| PLB   | 22%               |   |
| GR2   | 22%               |   |
| GR8   | 24%               |   |

Chi Square Analysis
PK-PD Correlation Between Human and Mouse Data

Change in HVPG Using PK Range Groups for GR8

<table>
<thead>
<tr>
<th>Group</th>
<th>Mean ± SEM</th>
<th>n</th>
</tr>
</thead>
<tbody>
<tr>
<td>PLB</td>
<td>-8%</td>
<td>54</td>
</tr>
<tr>
<td>GR8 (&lt;12K AUC)</td>
<td>-8%</td>
<td>25</td>
</tr>
<tr>
<td>GR8 (&gt;12K AUC)</td>
<td>+4%</td>
<td>27</td>
</tr>
</tbody>
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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

<table>
<thead>
<tr>
<th></th>
<th>GR2&lt;sup&gt;1&lt;/sup&gt;</th>
<th>GR8&lt;sup&gt;1&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hepatocyte Ballooning</td>
<td>0.04</td>
<td>0.05</td>
</tr>
<tr>
<td>NAFLD Activity Score</td>
<td>0.19</td>
<td>0.28</td>
</tr>
<tr>
<td>Ishak Stage</td>
<td>0.20</td>
<td>0.59</td>
</tr>
</tbody>
</table>

<sup>1</sup>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

- PLB: 6/33, 18%
- GR2: 0/25, 0%
- GR8: 1/23, 4%

p = 0.02
p = 0.12
$^{13}$C-Methacetin Breath Test for Quantitative Liver Function Analysis

$^{13}$C-Methacetin is exclusively metabolized through cytochrome P450 1A2 and $^{13}$CO$_2$ is exhaled

- Over 2500 patients tested
- MBT assesses the capability of the liver to metabolize (microsomal function)
- Methacetin has a high extraction ratio > 0.7

Patient exhaled breath is collected via a nasal cannula and measured by the BreathID®

C-Methacetin Breath Test in Patients Without Baseline Varices

- Evaluated at baseline and end of study (54 weeks)
- Measure was either improvement or worsening of methacetin breath test (MBT)
- Statistically significant difference between GR2 and placebo (PBO)
- No difference between GR8 and placebo (PBO)
- Similar pattern of results to HVPG and hepatocyte ballooning on liver biopsy
Conclusions From NASH-CX Clinical Trial

- Δ HVPG associated with GR treatment was not significant in total patient population, but was 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 Δ HVPG, percentage of responders, and development of new varices
  - Less pronounced effects of GR8 may be explained by its variable pharmacokinetics
- GR treatment improved hepatocyte ballooning in the total population, which correlated with an improvement in HVPG
- Improvement in $^{13}$C methacetin breath test mirrored Δ HVPG and hepatocyte ballooning
- 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
Possible Registration Endpoints in Compensated NASH Cirrhosis

- Non-Cirrhotic NASH
  - Reduced progression to complications
  - At least 1 stage reduction in fibrosis (NASH-CRN system) (reversal of cirrhosis)
  - Reduced progression to varices (surrogate vs. clinical endpoint)

- Compensated NASH Cirrhosis
  - No Varices
  - Varices
  - Improvement in HVPG (surrogate)

- Decompensated NASH Cirrhosis

Broad spectrum of non-invasive functional, structural, and serum tests should continue to be investigated for correlation to clinical outcomes of cirrhosis.
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