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

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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

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

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
  ▪ 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)

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)
## Study Demographics & Baseline Assessments

<table>
<thead>
<tr>
<th>Variable</th>
<th>Total (n=162)</th>
<th>Placebo (n=54)</th>
<th>GR2 (n=54)</th>
<th>GR8 (n=54)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age, years; median (IQR)</strong></td>
<td>59 (52, 65)</td>
<td>59 (53, 64)</td>
<td>60 (53, 65)</td>
<td>58 (51, 63)</td>
</tr>
<tr>
<td><strong>Female, n (%)</strong></td>
<td>113 (70)</td>
<td>36 (67)</td>
<td>34 (63)</td>
<td>43 (79)</td>
</tr>
<tr>
<td><strong>Non-Hispanic White, n (%)</strong></td>
<td>132 (81)</td>
<td>46 (85)</td>
<td>46 (85)</td>
<td>40 (74)</td>
</tr>
<tr>
<td><strong>BMI, kg/m²; median (IQR)</strong></td>
<td>34 (31, 39)</td>
<td>34 (30, 38)</td>
<td>36 (31, 41)</td>
<td>35 (31, 38)</td>
</tr>
<tr>
<td><strong>Diabetes, n (%)</strong></td>
<td>100 (62)</td>
<td>32 (59)</td>
<td>32 (59)</td>
<td>36 (67)</td>
</tr>
<tr>
<td><strong>AST (U/L) mean ± SD</strong></td>
<td>49.8 ± 33.8</td>
<td>51.9 ± 48.2</td>
<td>48.3 ± 23.0</td>
<td>49.3 ± 24.8</td>
</tr>
<tr>
<td><strong>ALT (U/L) mean ± SD</strong></td>
<td>47.1 ± 34.1</td>
<td>48.1 ± 38.1</td>
<td>42.4 ± 21.0</td>
<td>50.9 ± 40.1</td>
</tr>
<tr>
<td><strong>ELF Score mean ± SD</strong></td>
<td>10.7 ± 1.2</td>
<td>10.8 ± 1.1</td>
<td>10.7 ± 1.2</td>
<td>10.7 ± 1.2</td>
</tr>
<tr>
<td><strong>NAFLD Activity Score</strong></td>
<td>4.2 ± 1.6</td>
<td>4.2 ± 1.5</td>
<td>4.3 ± 1.3</td>
<td>4.2 ± 1.6</td>
</tr>
<tr>
<td><strong>Ishak Stage (5/6)</strong></td>
<td>48/123</td>
<td>13/41</td>
<td>20/43</td>
<td>15/39</td>
</tr>
<tr>
<td><strong>Collagen (%) mean ± SD</strong></td>
<td>10.5 ± 6.1</td>
<td>10.8 ± 6.5</td>
<td>9.7 ± 5.9</td>
<td>11.0 ± 6.1</td>
</tr>
</tbody>
</table>

IQR=interquartile range; BMI=body mass index; AST=aspartate transaminase; ALT=alanine transaminase; ELF=enhanced liver fibrosis; NAFLD=non-alcoholic fatty liver disease
There were no statistical differences between the three treatment groups for any of the measures. CSPH=clinically significant portal hypertension ($\geq 10$ mm Hg). MPH=mild portal hypertension ($\geq 6$ and $< 10$ mm Hg).

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

Total Patient Population

- Mean ± SEM
- ITT with LOCF (last observation carried forward); ANOVA with LSD (least squared difference)

Mild Portal Hypertension

- Mean ± SEM
- 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

mean ± SEM

Planned primary endpoint was a change of ≥15% in hepatopulmonary venous pressure gradient (HVPV) from baseline to week 54

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

A. Total Population

<table>
<thead>
<tr>
<th>Group</th>
<th>PLB</th>
<th>GR2</th>
<th>GR8</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cases</td>
<td>9/52</td>
<td>15/50</td>
<td>11/49</td>
</tr>
<tr>
<td>Percent Responders</td>
<td>17%</td>
<td>30%</td>
<td>22%</td>
</tr>
</tbody>
</table>

Chi Square Analysis

B. No Varices at Baseline

<table>
<thead>
<tr>
<th>Group</th>
<th>PLB</th>
<th>GR2</th>
<th>GR8</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cases</td>
<td>4/33</td>
<td>10/23</td>
<td>4/22</td>
</tr>
<tr>
<td>Percent Responders</td>
<td>12%</td>
<td>43%</td>
<td>18%</td>
</tr>
</tbody>
</table>

Chi Square Analysis

C. Varices at Baseline

<table>
<thead>
<tr>
<th>Group</th>
<th>PLB</th>
<th>GR2</th>
<th>GR8</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cases</td>
<td>5/23</td>
<td>5/23</td>
<td>7/29</td>
</tr>
<tr>
<td>Percent Responders</td>
<td>22%</td>
<td>22%</td>
<td>24%</td>
</tr>
</tbody>
</table>
PK-PD Correlation Between Human and Mouse Data

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

<table>
<thead>
<tr>
<th></th>
<th>GR2(^1)</th>
<th>GR8(^1)</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>

\(^1\)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\(^1\)

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

1. Development of new varices
2. Variceal hemorrhage
3. Clinically significant ascites
4. Overt hepatic encephalopathy

↑ CTP score ≥ 2
↑ MELD to ≥ 15
Liver transplantation or death
## Adverse Events

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

\(^1\) 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
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