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

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Background and Aims: Galectin-3 protein is implicated in the pathogenesis of NASH and toxin-induced fibrosis in animal models, both of which were improved by GR-MD-02, a novel gal-3 inhibitor. To test the safety and efficacy of GR-MD-02 in patients with NASH cirrhosis and PH.

Method: Phase 2B study randomized adults with NASH cirrhosis and portal hypertension (PH) to receive either placebo (PLB), or GR-MD-02 at 2 mg/kg (GR2), or GR-MD-02 at 8 mg/kg (GR8) in 26 biweekly intravenous infusions over 52 weeks. Eligibility criteria were HVPG ≥ 6 mmHg, no or small varices, NASH cirrhosis by biopsy, and no complications from cirrhosis. Primary endpoint was change in HVPG (Δ HVPG) at the end of treatment (EOT), compared to baseline (BL); secondary endpoints were changes in liver histology and the development of complications. Subgroup analyses were conducted in (a) no esophageal varices at BL and (b) mild PH (HVPG between ≥6 and <10 mmHg) at BL.

Results: 162 patients were randomized to receive PLB (n=54), GR2 (n=54), or GR8 (n-54). BL demographic, clinical, and laboratory characteristics were similar among the 3 groups. Baseline HVPG (mmHg) was 11.6 ± 4 in PLB, 12.3 ± 4.3 in GR2, and 12.7 ± 4.2 GR8 groups. 81 patients had no esophageal varices at BL (33 PLB, 25 GR2, and 23 in GR8) and 53 had mild PH (20 PLB, 17 GR2, and 16 in GR8).

The total patient population had no statistically significant difference in Δ HVPG between PLB and GR (Δ PLB = 0.3 mmHg, Δ GR2 = -0.37 mmHg, Δ GR8 = -0.42 mmHg). There was no effect on fibrosis or NAFLD Activity Score, but there was a statistically significant improvement in hepatocyte ballooning with GR2 (p=0.03) and a trend with GR8 (p=0.09) versus PLB.

In patients without varices, there was a significant difference in ΔHVPG between PLB and GR2 (PLB=0.8 mmHg, GR-2=-1.08 mmHG, p<0.01 vs PLB) but not with GR8 (-0.42 mmHg), p=0.36 vs PLB). Also, significantly fewer patients receiving active treatment developed new varices at E0T (PLB 6, GR2=0 (p=0.02) and GR8=1 (p=0.12) and for combined treatment groups versus PLB (p=0.01). In mild PH, there was a significant difference in ΔHVPG between PLB and both treated groups (PLB=1.7 mmHg, GR2=-0.2, p=0.055 vs PLB, GR8=-0.2, p=0.036 vs PLB). Responder analysis, defined as the percent who had both ↓HVPG ≥ 2 mmHg and ≥ 20% ↓HVPG was significantly higher in GR2 (13% PLB vs. 43% in GR-2, p=0.01) but not GR8 (18%, p=ns). GR2 and GR8 were well tolerated with similar proportion of AEs and SAEs; more patients discontinued GR8 with AE (n=5), 0 in PLB or GR2.

Conclusion: GR-MD-02 did not improve HVPG or liver fibrosis in the entire study population, but significantly improved hepatocyte ballooning. Significant and clinically relevant beneficial effects of GR2 were evident in NASH cirrhosis without varices, or those with mild PH. Significantly fewer GR2 patients developed new varices at EOT. These data warrant further investigating GR-MD-02 in patients with NASH cirrhosis without varices.