according to 2 time frames: first 24 months and between M24 months and M84. A total of 240 patients were included in 3 groups: A: patients transplanted for AH (n = 68); B: patients transplanted for alcohol-related cirrhosis and 6 months of abstinence (n = 93); C: patients with AH, not transplanted (n = 47).

Results: The rate of any alcohol relapse, whatever the amount consumed, was not different between groups A and B, either during the first 24 months (HR 1.56, 95%CI: 0.87–2.76, p = 0.13) or between M24 and M84 (HR 1.23, 95%CI: 0.48–3.13, p = 0.66). The rate of heavy alcohol relapse (defined by ≥30 g/d in women and ≥40 g/d in men) was higher in group A than in group B at M24 (23.5 vs. 5.4%, HR 4.86, 95%CI: 1.78–13.2, p = 0.002) but was not different between M24 and M84 (34.3 vs. 16.7%, HR 1.17, 95%CI: 0.44–3.07, p = 0.76). There was a trend toward better survival at M84 in patients transplanted for AH (group A) vs. group B: 83.2 (A) vs. 70% (B), HR = 0, 34, 95%CI: 0.11–1.02, p = 0.054). Rejection rates after LT were not different between the two groups (2.9 vs. 3.2%, p = 0.9) but incidence of de novo alcohol-related cirrhosis was higher in group A (11.8 vs. 3.2%, p = 0.03) while incidence of cancers was more important in group B (22.6 vs. 8.8%, p = 0.02). Among all patients with AH, patients selected for LT (group A) had a better survival at 84 months than non-selected patients (group C): 64 vs. 13%, HR = 4, 2.5–6.67, p < 0.001).

Conclusion: Rates of alcohol relapse between M24 and M84 are similar between patients transplanted for AH and those with alcohol-related cirrhosis selected with the 6-month rule. Heavy alcohol relapse mostly occurs during the first 2 years in AH without significant differences between the two groups thereafter. Early alcohol management should be proposed after LT for AH. Patients transplanted for alcohol-related cirrhosis tend to have a lower long-term survival.

GS-012

Novel DGAT2 antisense inhibitor demonstrates significant MASH resolution in biopsy-proven F2/F3 MASH: results from a 51-week multicenter randomized double-blind placebo-controlled phase 2 trial

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Background and aims: ION224 is an investigational ligand-conjugated antisense medicine designed to reduce the production of diacylglycerol acyltransferase 2 (DGAT2), an enzyme that catalyzes the final step in hepatic triglyceride synthesis. ION224-CS2 was an adaptive Phase 2 trial to study the safety and efficacy of monthly subcutaneous injections of ION224 in biopsy-proven MASH patients with MASLD activity score (NAS) ≥4 and baseline MRI-PDFF≥10%. The primary end point was improvement in steatohepatitis at Week 51 as measured by ≥2-point reduction in NAS with ≥1-point improvement in hepatocellular ballooning or lobular inflammation, and without worsening of fibrosis. An analysis of the primary end point along with key secondary end points was conducted.

Method: The study enrolled 160 patients to receive monthly doses of ION224 or placebo during a 49-week treatment period. In Part 1, 93 patients were randomized to three dose cohorts to receive either 60, 90, or 120 mg of ION224 or placebo (3:1). Based on a pre-specified interim analysis at 3 months, 2 of the 3 dose cohorts were selected by DSMB for expanded enrollment, based on safety and hepatic MRI-PDFF analysis. In Part 2, an additional 67 patients were randomized 1:1 into each of the two expanded dose cohorts (90 and 120 mg) and then in a 2:1 ratio to receive either ION224 or placebo within each cohort.

Results: Baseline characteristics included age 53 (12) (mean (SD)), BMI 37.8 (7.1), type 2 diabetes 50.6%, MRI-PDFF (%) 22.4 (7.4), baseline fibrosis stage: F2-49.6%, F3-39.1%. The primary end point of ≥2-point reduction in NAS was met in both expanded cohorts in 58.8% and 46.2% of patients treated with ION224 120 mg or 90 mg, respectively, compared to 18.8% for placebo (n = 34, p <0.001 and n = 39, p = 0.015, respectively, placebo n = 32). Subgroup analysis indicated that significant improvements in the primary end point were observed in patients with both F2 and F3 fibrosis. Additionally, 35.6% of patients treated with 120 mg or 90 mg achieved MASH resolution without worsening of fibrosis versus 15.6% for placebo (p = 0.039). Further, 32.4% of patients treated with 120 mg achieved ≥1 stage improvement in fibrosis without worsening steatohepatitis versus 12.5% for placebo. Forty-four (44) % of patients treated with 120 mg achieved ≥50% relative reduction in liver steatosis by MRI-PDFF vs 3% of placebo (p <0.001). ION224 was safe and well-tolerated. There were no treatment-related SAEs, no GI side effects or worsening of hepatic or renal function or plasma lipids (including no hypertriglyceridemia) after ION224 treatment.

Conclusion: This study provides the first clinical evidence that reduction of hepatic fat after DGAT2 inhibition leads to MASH resolution. ION224 was safe and well-tolerated in this study with once-monthly subcutaneous dosing. These data support the potential for ION224 treatment to provide benefit to patients with MASH and liver fibrosis.

Late-breaker Orals

LBO-001

Tirzepatide for the treatment of metabolic dysfunction-associated steatohepatitis with liver fibrosis: results of the SYNERGY-NASH phase 2 trial

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Background and aims: Metabolic dysfunction-associated steatohepatitis (MASH) is a progressive liver disease associated with liver-related morbidity and mortality. This study evaluated the efficacy and safety of tirzepatide, a dual agonist of the glucose-dependent insulinotropic polypeptide and glucagon-like-peptide-1 receptors, in the treatment of non-cirrhotic MASH with significant liver fibrosis.

Method: SYNERGY-NASH (NCT04166773) was a multicenter, double-blind, randomized, placebo (PBO)-controlled Phase 2 dose-finding trial in patients with biopsy-confirmed MASH, stage 2 or 3 fibrosis and a non-alcoholic fatty liver disease activity score (NAS) ≥4. Participants (n = 190) were randomly assigned 1:1:1:1 to receive once-weekly s.c. tirzepatide (5 mg, 10 mg or 15 mg) or PBO for 52 weeks. The primary end point was MASH resolution without worsening of fibrosis at 52 weeks. Secondary end points included fibrosis improvement by ≥1 stage without worsening of MASH and a reduction in NAS by ≥2 points with ≥1 point reduction in at least 2 NAS components. Efficacy results were analyzed with the intent to treat population using multiple imputation for missing data.

Results: End-of-treatment liver biopsies were available for 157 participants. The proportion of participants who achieved MASH resolution without worsening of fibrosis was 9.8% for PBO, 43.6% for tirzepatide 5 mg, 55.5% for tirzepatide 10 mg and 62.4% for