Effects of zalfermin, cagrilintide, and semaglutide on non-invasive fibrosis biomarkers in alcohol-related liver disease: A phase 2 randomized trial

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Aim

- To assess the effects of fibroblast growth factor 21 (FGF21; zalfermin), glucagon -like peptide-1 (GLP-1; semaglutide), and amylin (cagrilintide) receptor agonists on fibrosis-related disease activity in alcohol-related liver disease (ALD).

Introduction

- ALD is a leading cause of liver-related mortality. Sustained alcohol abstinence is central to management but difficult to achieve, and no approved therapies target the underlying fibrogenic process.
- FGF21 and GLP-1 receptor agonists improve steatohepatitis, liver fibrosis, and systemic metabolic health,[1–3] and may also reduce alcohol intake via modulation of reward-related brain regions.[4–6]

Methods

- This was a proof-of-concept, phase 2, multinational, randomized, double-blind, placebo-controlled trial evaluating the effect of once-weekly subcutaneous zalfermin 30 mg, cagrilintide 2.4 mg, and semaglutide 2.4 mg alone or in select combinations versus placebo on markers of liver fibrosis and alcohol use (NCT06409130).
- Eligible participants were aged ≥18 years, had a BMI >25 kg/m², a ≥5-year history of unhealthy alcohol consumption (mean of ≥50 grams per day for males and ≥40 grams per day for females in the preceding year), and an Enhanced Liver Fibrosis (ELF) score of ≥9.0.
- The primary endpoint was change in ELF score from baseline to week 28.
- Secondary endpoints evaluated after 28 weeks of treatment included change in liver stiffness measured by vibration-controlled transient elastography (VCTE-LSM), N-terminal propeptide of type III collagen (PRO-C3), alcohol use assessed by Timeline Follow-Back (TLFB), and safety.

Table 1. Baseline characteristics

	Zalfermin 30 mg	Semaglutide 2.4 mg	Zalfermin 30 mg + semaglutide 2.4 mg	Cagrilintide 2.4 mg	Cagrilintide 2.4 mg + semaglutide 2.4 mg	Placebo	Total
Number of participants	45	43	46	46	46	44	**270**
Age, years – mean (SD)	57.1 (9.9)	59.7 (10.1)	59.2 (9.5)	62.1 (9.4)	59.9 (10.4)	60.1 (11.0)	**59.7 (10.1)**
Sex, female – n (%)	10 (22.2)	9 (20.9)	9 (19.6)	14 (30.4)	16 (34.8)	12 (27.3)	**70 (25.9)**
BMI, kg/m² – mean (SD)	31.5 (4.4)	33.1 (7.0)	32.3 (5.0)	32.1 (5.1)	33.0 (5.4)	32.4 (5.4)	**32.4 (5.4)**
Type 2 diabetes – n (%)	12 (26.7)	13 (30.2)	11 (23.9)	13 (28.3)	11 (23.9)	11 (25.0)	**71 (26.3)**
ELF – mean (SD)	10.1 (0.8)	10.2 (1.2)	10.4 (1.1)	10.0 (0.8)	10.1 (1.0)	10.2 (0.9)	**10.2 (1.0)**
VCTE-LSM, kPa – geometric mean (CV)	9.3 (60.9)	9.7 (55.8)	11.9 (66.4)	8.8 (54.2)	10.8 (53.9)	10.3 (63.7)	**10.1 (59.7)**
TLFB at screening, g/day – mean (SD)	86 (63)	85 (73)	79 (38)	75 (42)	79 (49)	80 (52)	**81 (53)**

BMI, body mass index; CV, coefficient of variation; ELF, Enhanced Liver Fibrosis; g/day, grams per day; SD, standard deviation; TLFB, Timeline Follow-Back; VCTE-LSM, vibration-controlled transient elastography liver stiffness measurement.

Results

- A total of 270 participants were randomized: 25.9% were female, the mean age was 59.7 years, the mean body mass index (BMI) was 32.4 kg/m², and 26.3% had type 2 diabetes (**Table 1**).
- Baseline alcohol use was substantial, with a mean TLFB of 81 grams per day; mean ELF score was 10.2 and geometric mean VCTE-LSM was 10.1 kPa (**Table 1**).
- The primary endpoint of change in ELF score was met for all active treatments (**Figure 1A**)
- Other fibrosis-related measures generally supported the ELF findings, although treatment effects were not uniformly statistically significant (**Figures 1B and 1C**).
- Although a trend for decreased alcohol consumption was observed in all treatment groups, no significant differences versus placebo were observed for TLFB (**Figure 1D**).
- No unexpected safety signals were identified. Gastrointestinal adverse events predominated, and adverse events leading to treatment discontinuation occurred numerically more frequently in the combination groups than with placebo (**Figure 2**).

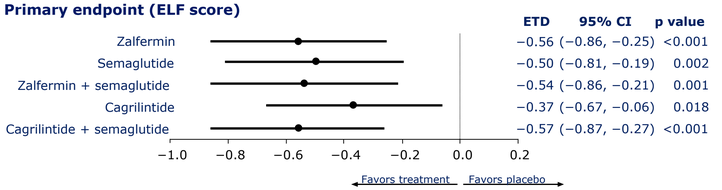
Conclusions

- These findings provide proof-of-concept evidence for pharmacological effects on fibrosis-related disease activity in ALD and support further evaluation in larger, longer-term trials.

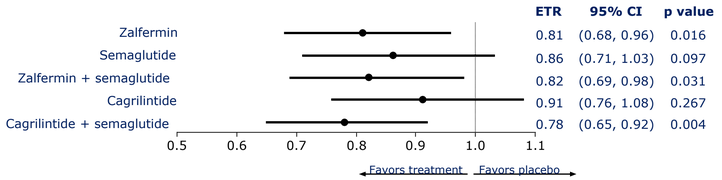
Figure 1. Estimated treatment effects after 28 weeks of treatment

KEY RESULT

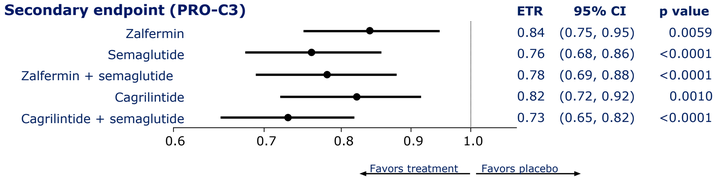
A. Primary endpoint (ELF score)



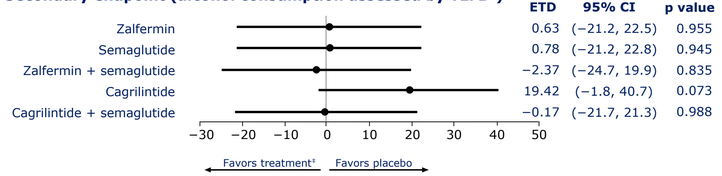
B. Secondary endpoint (VCTE-LSM)



C. Secondary endpoint (PRO-C3)

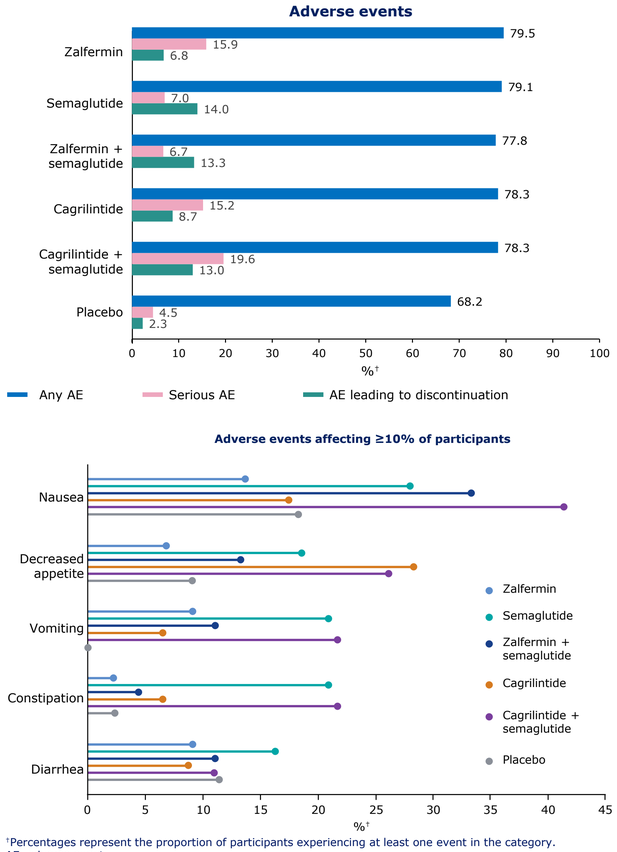


D. Secondary endpoint (alcohol consumption assessed by TLFB†)



†Average alcohol consumption during the previous 28 days, expressed as grams per day (1 unit = 14 grams of alcohol).
‡Alcohol consumption decreased from baseline across all treatment groups, including placebo. ETDs represent differences versus placebo and do not reflect within-group changes from baseline; values to the left of zero indicate a greater reduction in alcohol consumption versus placebo. CI, confidence interval; ELF, Enhanced Liver Fibrosis; ETD, estimated treatment difference; ETR, estimated treatment ratio; PRO-C3, N-terminal propeptide of type III collagen; TLFB, Timeline Follow-Back; VCTE-LSM, vibration-controlled transient elastography liver stiffness measurement.

Figure 2. Safety profile and adverse events



†Percentages represent the proportion of participants experiencing at least one event in the category.
AE, adverse event.

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