Reproducible and clinically translatable hepatoprotective effects of tirzepatide in the GAN diet-induced obese and biopsy-confirmed mouse model of MASH

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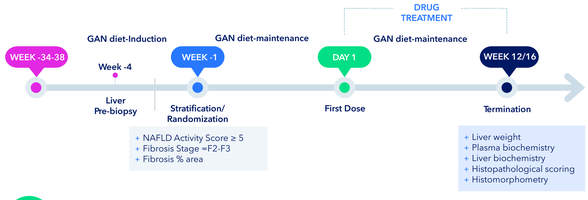
Background & Aim

The glucagon-like peptide-1 receptor (GLP-1R) and gastric inhibitory polypeptide receptor (GIPR) dual agonist tirzepatide is currently approved for the treatment of obesity and type 2 diabetes. In a recent phase 2b trial (SYNERGY-NASH) in patients with metabolic-dysfunction associated steatohepatitis (MASH), tirzepatide showed a significant effect on MASH resolution without worsening fibrosis after 52 weeks (Loomba et al., NEJM, 2024).

Methods

Tirzepatide was profiled in 4 individual GAN DIO-MASH mouse studies with identical design. C57BL/6JRj mice were fed the GAN diet high in saturated fat, fructose, and cholesterol for 34-38 weeks before treatment start. Only animals with biopsy-confirmed NAFLD Activity Score (NAS) ≥5 points and moderate/advanced fibrosis (stage =F2-F3) were included and stratified into treatment groups. GAN DIO-MASH mice (n=18 per group) received tirzepatide (Tirz, 10 nmol/kg, SC) or vehicle (Veh, SC) once daily for 12 weeks (study 1 and 2) or 16 weeks (study 3 and study 4). Vehicle-dosed chow-fed controls served as healthy controls (Lean). Within-subject comparisons (pre- vs. post-treatment) were performed for NAS and fibrosis stage by Gubra Histopathological Objective Scoring Technique (GHOST). Terminal quantitative endpoints included plasma/liver biochemistry an quantitative liver histology. Furthermore, histopathological pre-to-post assessment of N AS and fibrosis stage were evaluated against primary histological endpoints applied in a corresponding clinical trial, (i.e. resolution of MASH with no worsening of liver fibrosis; at least 1-stage fibrosis improvement without worsening of MASH). Statistical analyses were performed using Dunnett's test one-factor linear model (individual studies), Fisher's exact test (pooled study data on semiquantitative histopathological scoring variables) or one-way ANOVA with Dunnett's post-hoc test (pooled study data on quantitative endpoints), respectively. *p<0.05, **p<0.01, ***p<0.001 compared to corresponding vehicle controls.

1 Study outline



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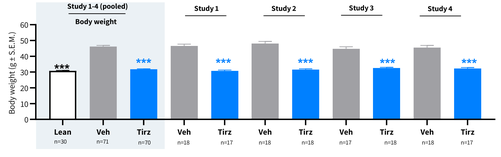
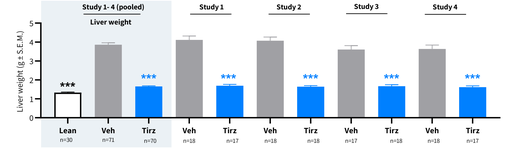
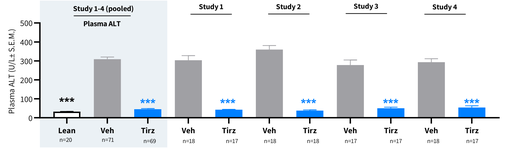
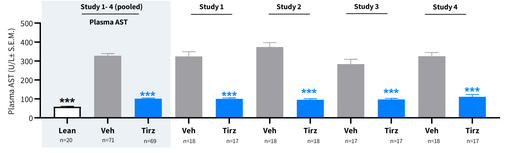


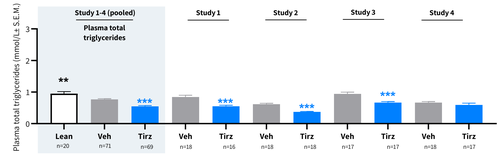
3 Liver weight & transaminases

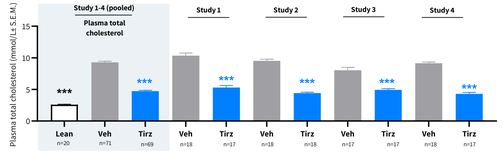




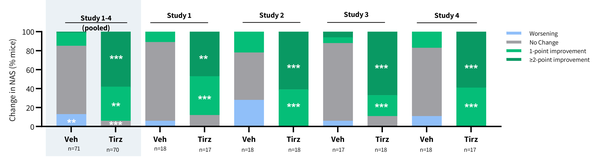


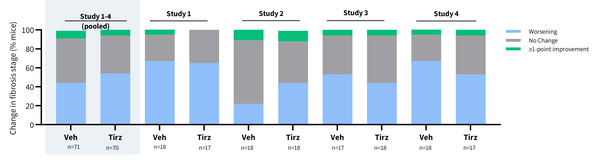
4 Plasma total cholesterol & triglycerides



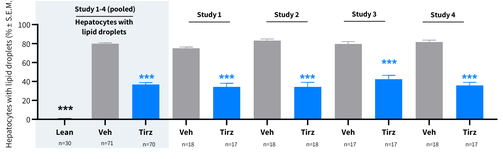


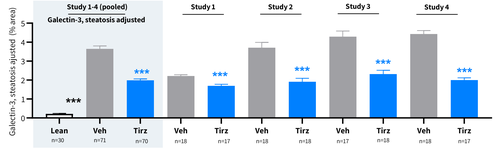
5 NAFLD Activity Score (NAS) & Fibrosis stage

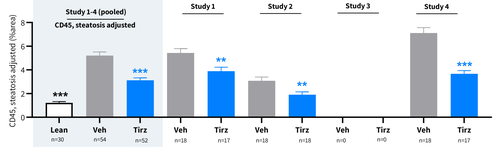


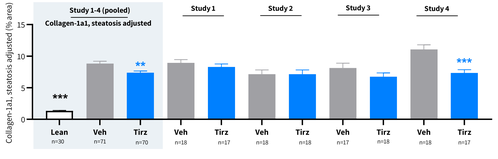


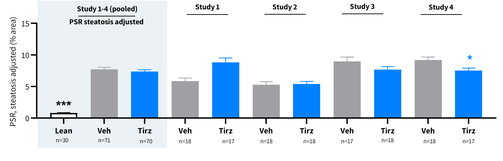
6 Quantitative histological markers of steatosis, inflammation, fibrosis and fibrogenesis

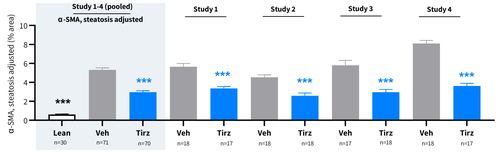




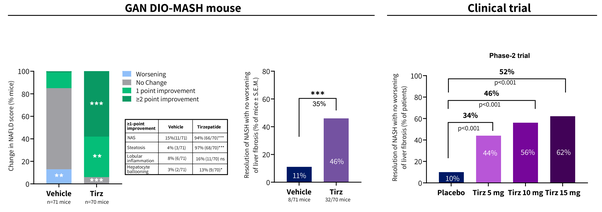


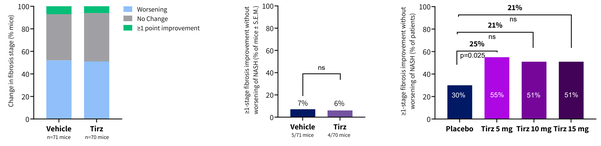






7 Clinical translatability





Conclusion

Shorter-term tirzepatide therapy in GAN DIO-MASH mice:

- **Improves body weight, hepatomegaly, transaminases and hypercholesterolemia**
- **Improves NAFLD Activity Score and quantitative histological markers of steatosis and inflammation**
- **Does not improve Fibrosis Stage or quantitative histological markers of fibrosis**
- **Improves quantitative histological marker of fibrogenesis, indicating longer treatment intervention might demonstrate anti-fibrotic action**

Histological outcomes of tirzepatide treatment in GAN DIO-MASH mice are comparable in terms of NASH resolution to Phase-2 (SYNERGY-NASH) clinical trial.

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