Comparative anti-fibrotic efficacy of resmetirom, semaglutide, tirzepatide and efruxifermin in the GAN diet-induced obese and biopsy-confirmed mouse model of MASH

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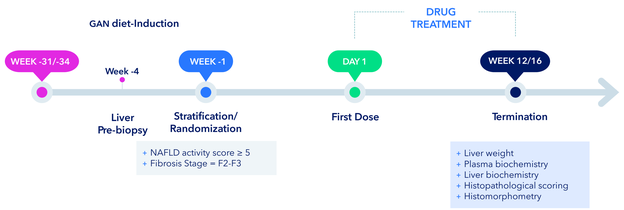
Background & Aim

Resmetirom (RES, THR-βR agonist) has recently been FDA-approved for the treatment of metabolic dysfunction-associated steatohepatitis (MASH). Other drug concepts are in late-stage clinical development for MASH, including semaglutide (SEMA, GLP1R agonist), tirzepatide (TZP, GLP1R-GIPR co-agonist) and efruxifermin (EFX, FGF21 analogue). The present study aimed to compare the efficacy of RES, SEMA, TZP and EFX monotherapy on metabolic, biochemical and histopathological outcomes in the translational Gubra Amylin NASH (GAN) diet-induced obese and biopsy-confirmed mouse model of MASH with moderate/advanced liver fibrosis.

1 Study outline



Group	Animal	Gender	Number of animals 12W/16W study	Treatment	Administration route	Dosing Frequency	Dosing concentration
1	LEAN-CHOW	Male	10	**Vehicle**	SC	QD	-
2	DIO-MASH	Male	49 / 54	**Vehicle (VEH)**	SC / PO	QD/QW	-
3	DIO-MASH	Male	16 / 19	**Resmetirom (RES)**	PO	QD	3 mg/kg
4	DIO-MASH	Male	16 / 17	**Semaglutide (SEMA)**	SC	QD	30 (12w) nmol/kg 10 (16w) nmol/kg
5	DIO-MASH	Male	18 / 18	**Tirzepatide (TZP)**	SC	QD	10 nmol/kg
6	DIO-MASH	Male	18 / 18	**Efruxifermin (EFX)**	SC	QW	1 mg/kg

Figure 1. Study outline. SC; Subcutaneous, PO; Per oral, QD; Once Daily, QW; Once Weekly; GAN; Gubra Amylin NASH, DIO; Diet-induced obesity.

2 Metabolic and biochemical parameters

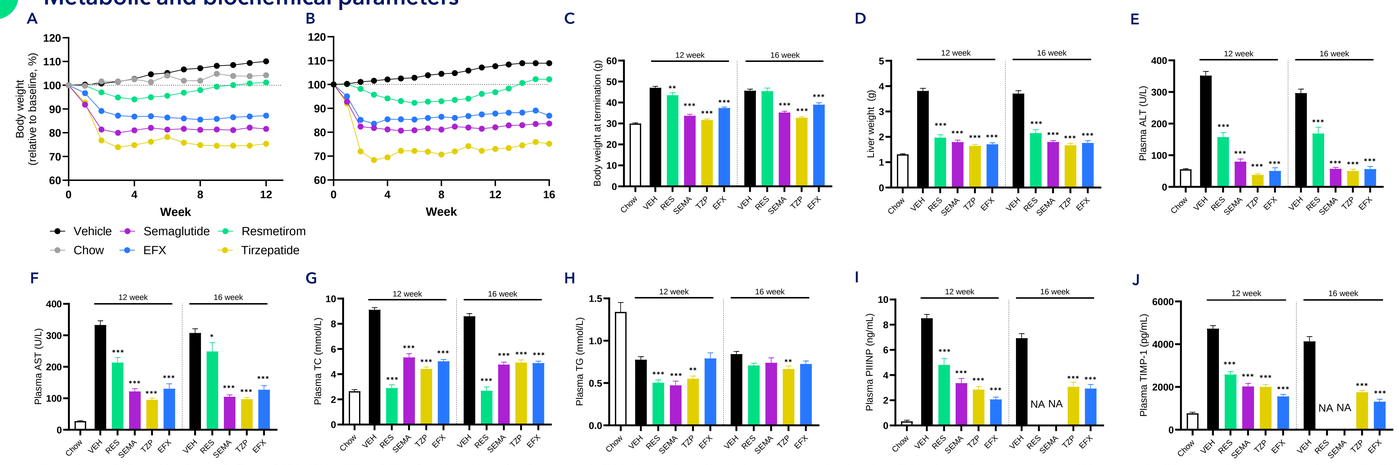


Figure 2. Metabolic and biochemical effects of RES, SEMA, TZP and EFX after 12 or 16 weeks of treatment. (A/B) Body weight profile (% change compared to baseline). **(D)** Body weight at termination (g). **(D)** Liver weight. **(E)** Plasma alanine aminotransferase (ALT). **(F)** Plasma aspartate transferase (AST). **(G)** Plasma total cholesterol (TC). **(H)** Plasma triglycerides (TG). **(I)** Plasma PIIINP. **(J)** Plasma TIMP-1.). *p<0.05, **p<0.01, ***p<0.001 compared to vehicle control (Dunnett's test one-factor linear model).

3 NAFLD Activity Score and Fibrosis Stage

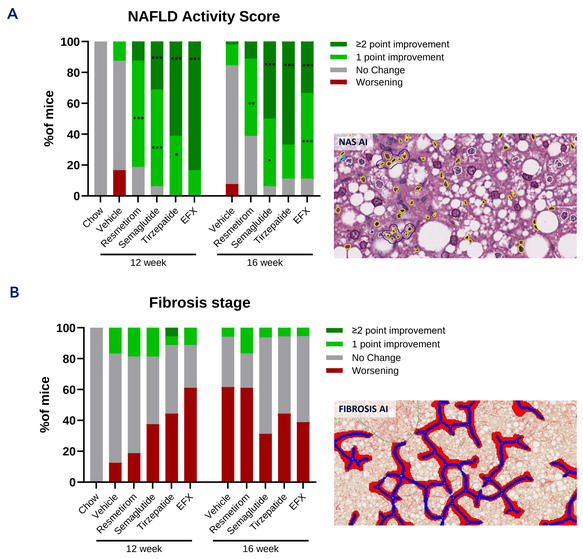


Figure 3. RES, SEMA, TZP and EFX improve NAFLD Activity Score (NAS) in GAN DIO-MASH mice. Histopathological scores were determined by Gubra Histopathological Objective Scoring Technique (GHOST) deep learning-based image analysis. **(A)** NAFLD Activity Score (NAS). **(B)** Fibrosis stage. *p<0.05, **p<0.01 ***p<0.001 compared to vehicle control (one-sided Fisher's exact test).

4 Histological markers of steatosis, inflammation, fibrosis and fibrogenesis

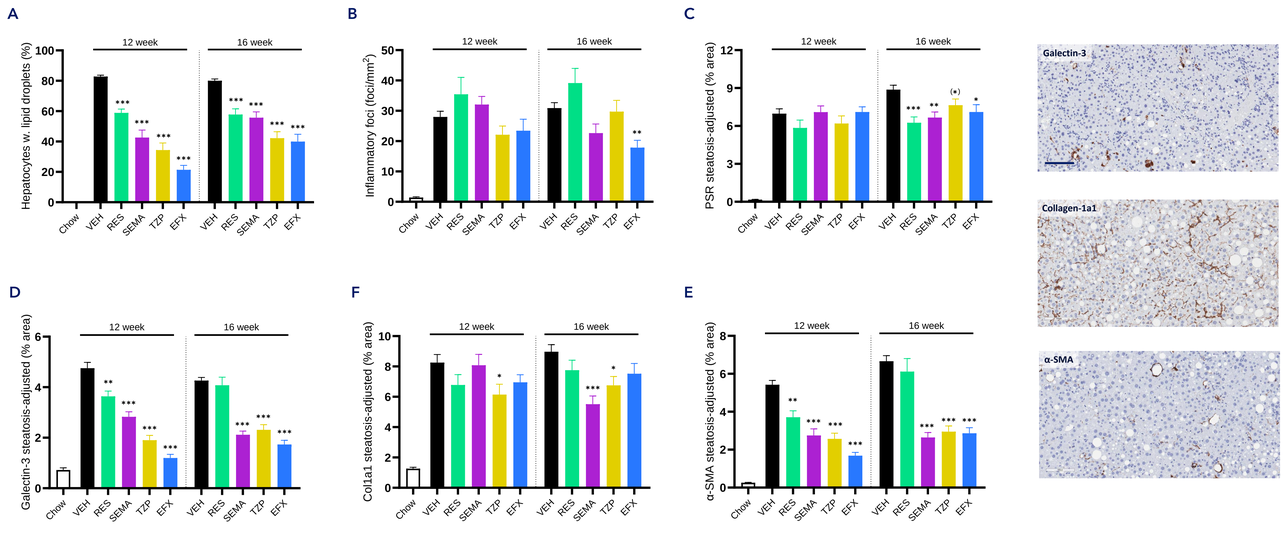


Figure 4. RES, SEMA, TZP and EFX improve quantitative histological endpoints. Histomorphometric assessments were performed by GHOST deep learning-based image analysis on scoring-associated variables (panels A-B) and conventional IHC image analysis (panels C-F), respectively. **(A)** % hepatocytes with lipid droplets. **(B)** Number of inflammatory foci. **(C)** % area of PSR (steatosis-adjusted). **(D)** % area of galectin-3 (steatosis-adjusted). **(E)** % area of collagen-1a1 (Col1a1, steatosis-adjusted) **(F)** % area of alpha-smooth muscle actin (α-SMA, marker of stellate cell activation; steatosis-adjusted). (*)p<0.10, *p<0.05, **p<0.01, ***p<0.001 compared to vehicle control (Unpaired t-test or Dunnett's test one-factor linear model). Right panels: Representative photomicrographs of galectin-3, Col1a1 and α-SMA (scale bar, 100 µm).

Conclusion

- EFX, SEMA and TZP reduced body weight while all treatments reduced hepatomegaly, plasma total cholesterol and plasma liver enzymes.
- All treatments improved NAFLD Activity Score independent of treatment duration.
- Benefits on NAFLD Activity Score were supported by quantitative liver histology for steatosis and inflammation.
- RES, SEMA, TZP and EFX did not improve Fibrosis Stage.
- Parenchymal collagen %-area (PSR and/or Col1a1a) was significantly reduced after 16 weeks of treatment with RES, SEMA, TZP and EFX.
- Antifibrotic efficacy was supported by corresponding reductions in fibrogenesis biomarkers, including plasma TIMP-1/PIIINP and liver α-SMA.

Longer treatment intervention promotes histological improvement in fibrosis, highlighting the importance of treatment duration to alleviate fibrosis burden in the GAN DIO-MASH model

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