Superior Hepatoprotective Effects of OPK-88006, a Novel GLP-1/Glucagon receptor dual agonist, to Semaglutide and Survodutide in the GAN Diet-Induced Obese and Biopsy-Confirmed Mouse Model of MASH

Authors

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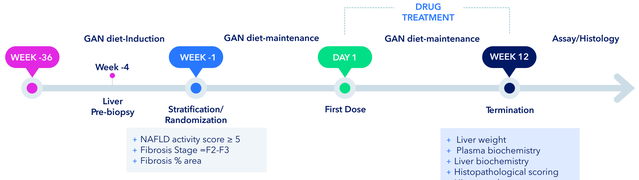
Background & Aim

OPK-88006 is a novel peptide-based, long-acting glucagon-like peptide-1 receptor (GLP1R)/glucagon receptor (GCGR) dual agonist in current preclinical development for metabolic diseases, including obesity and metabolic dysfunction-associated steatohepatitis (MASH).

The present study aimed to compare the therapeutic profile of OPK-88006, semaglutide (GLP1R monoagonist) and survodutide (dual GLP1R-GCGR agonist) in the translational Gubra Amylin NASH (GAN) diet-induced obese (DIO) and biopsy-confirmed mouse model of MASH with liver fibrosis.

1 Study outline



Group	Animal	Gender	Number of animals	Treatment	Administration route	Dosing Frequency	Dosing Administered
1	LEAN-CHOW	Male	10	**Vehicle**	SC	QD	0
2	DIO-MASH	Male	17	**Vehicle**	SC	QD	0
3	DIO-MASH	Male	17	**Semaglutide**	SC	QD	30nmol/kg
4	DIO-MASH	Male	15	**Survodutide**	SC	QD	15nmol/kg*
5	DIO-MASH	Male	18	**OPK-88006 - High**	SC	QD	20nmol/kg
6	DIO-MASH	Male	17	**OPK-88006 - Low**	SC	QD	10nmol/kg

Figure 1. Study outline. SC: Subcutaneous, QD; Once daily; GAN; Gubra Amylin NASH. *Survodutide initial starting dose of 20nmol/kg , being reduced to 15nmol/kg on day 10 and for the rest of the study period.

2 Metabolic and biochemical parameters

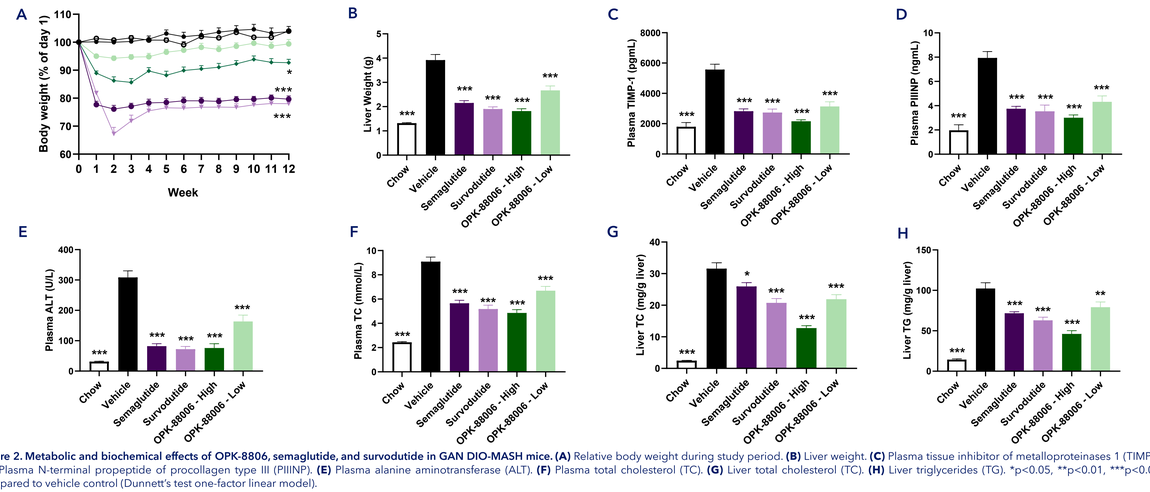


Figure 2. Metabolic and biochemical effects of OPK-8806, semaglutide, and survodutide in GAN DIO-MASH mice. (A) Relative body weight during study period. **(B)** Liver weight. **(C)** Plasma tissue inhibitor of metalloproteinases 1 (TIMP-1). **(D)** Plasma N-terminal propeptide of procollagen type III (PIIINP). **(E)** Plasma alanine aminotransferase (ALT). **(F)** Plasma total cholesterol (TC). **(G)** Liver total cholesterol (TC). **(H)** Liver triglycerides (TG). *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

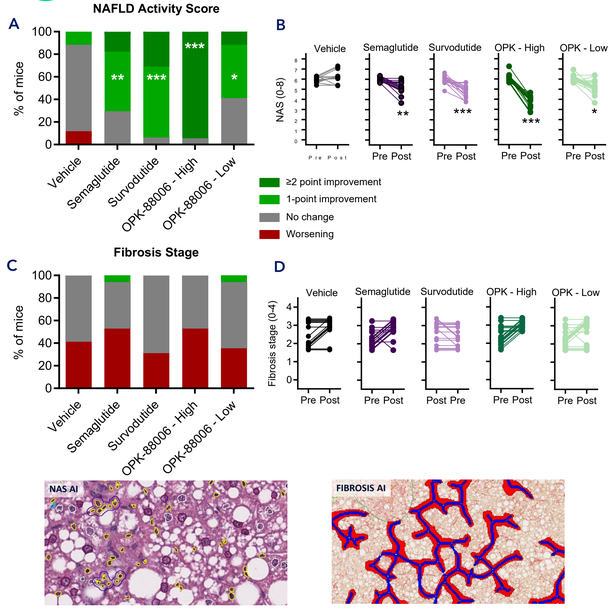


Figure 3. OPK-8806, semaglutide and survodutide improve NAFLD Activity Score in GAN DIO-MASH mice Histopathological scores were determined by Gubra Histopathological Objective Scoring Technique (GHOST) deep learning-based image analysis. **(A)** NAFLD Activity Score (NAS). **(B)** Individual pre-post NAS. **(C)** Fibrosis stage. **(D)** Individual pre-post fibrosis stage. **p<0.01, ***p<0.001 compared to vehicle (One-sided Fisher's exact test).

4 Histological markers of steatosis, inflammation, fibrosis and fibrogenesis

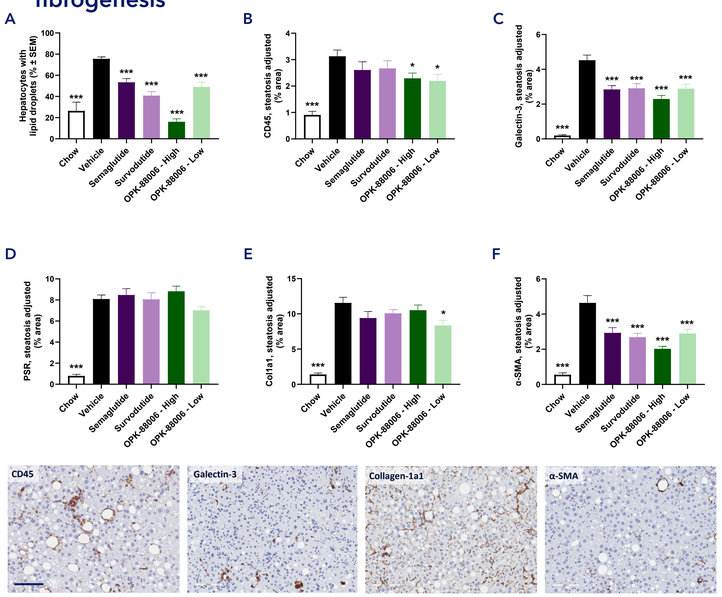


Figure 4. OPK-8806, semaglutide, and survodutide improves quantitative histological endpoints. Histomorphometric assessments were performed by GHOST deep learning-based image analysis on scoring-associated variables (panels A-B) and conventional IHC image analysis (panels C-F). **(A)** % hepatocytes with lipid droplets. **(B)** % area of CD45 (steatosis-adjusted). **(C)** % area of galectin-3 (steatosis-adjusted). **(D)** % area of PSR (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<0.05, ***p<0.001 compared to vehicle control (Dunnett's test one-factor linear model). Bottom panels: Representative photomicrographs of CD45 Gal-3, Col1a1 and α-SMA (scale bar, 100 µm).

5 Hepatic transcriptome analysis

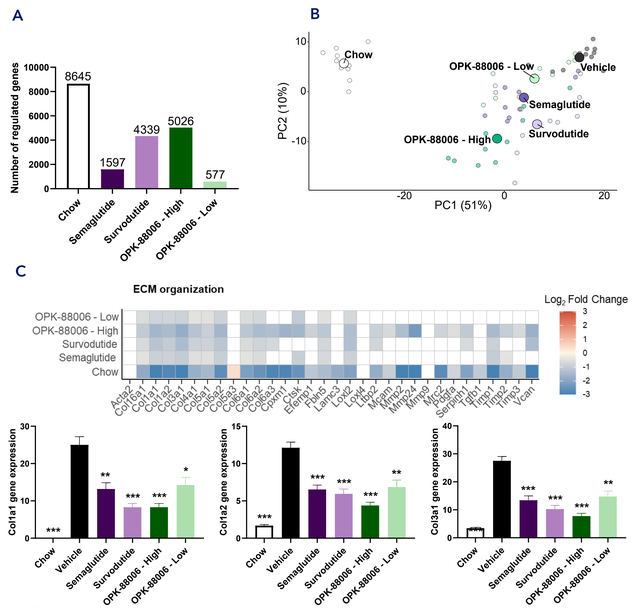


Figure 5. Hepatic transcriptome signatures following OPK-8806, semaglutide, and survodutide therapy.
(A) Total number of differentially expressed genes. **(B)** principal component analysis based on the top 500 most varying genes across the dataset **(C)** Regulation of gene expression in the extracellular matrix (ECM). Log2 fold change is indicated for significantly regulated genes (p_{adj} < 0.05 after correcting for multiple testing). *p<0.05, **p<0.01, ***p<0.001 . Red and blue colours indicate up- and down-regulation, respectively, compared to Vehicle.

Conclusion

- OPK-88006 (20nmol/kg), Semaglutide (30nmol/kg) and Survodutide (15nmol/kg) reduced body weight in GAN DIO-MASH mice, with superiority for Semaglutide and Survodutide.
- All treatments similarly improved hepatomegaly, plasma transaminase and plasma/liver lipids levels.
- All treatments improved NAFLD Activity Score, with OPK-88006 showing supiority to both Semaglutide and Survodutide.
- The therapeutic benefits of OPK-88006 on quantitative histological hallmarks of MASH (steatosis, inflammation) were superior to Semaglutide and Survodutide.
- All treatments reduced quantitative histology for fibrogenesis.
- All treatments impacted transcriptomic profile and significantly modulated gene expression markers for ECM and fibrosis.
- OPK-88006 is a promising GLP-1/Glucagon receptor dual agonist for the treatment of MASH

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