

Comparative Efficacy of INT-767 vs. Liraglutide in Gubra AMLN Mice

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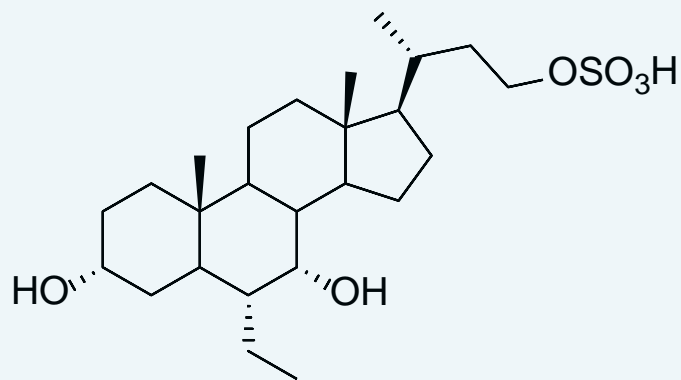
Gubra AMLN NASH Model vs. FLINT

Endpoint	FLINT (Vehicle Group @ Baseline)		<i>Lep^{ob/ob}</i> mice on AMLN diet (Vehicle Group @ Baseline)
<i>Fibrosis Score</i>	1.9		2.3
<i>NAS</i>	5.3		6.3
<i>Steatosis Score</i>	2.1		3
<i>Inflammation Score</i>	Lobular = 1.8	Portal = 1.2	2.3
<i>Ballooning Score</i>	1.4		1.0

- Based upon ALIOS high-trans fat diet (Tetri et al. 2008) with a few modifications:
 - Fructose included in the diet vs. drinking water
 - Diet in *Lep^{ob/ob}* vs. C57 Bl6
 - Mice are biopsied and those with a baseline NASH phenotype are “enrolled”

Background and Rationale

INT-767



- Bile acid analog
- FXR/TGR5 *in vitro* dual agonist
- Oral administration
- Early development (Phase 1)
- Improves metabolism and fibrosis in animal models

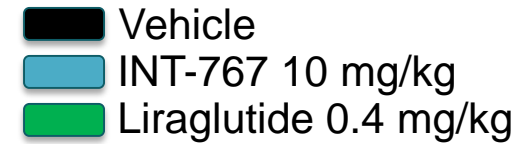
Liraglutide



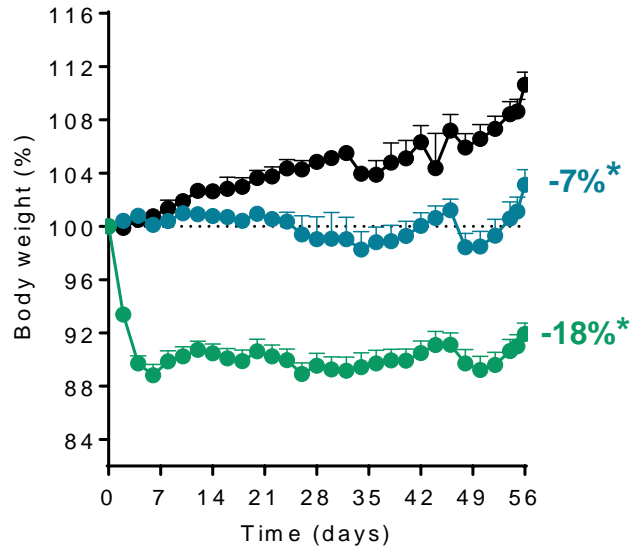
- Acylated Glucagon-like peptide
- GLP-1R agonist class
- Injectable administration (QD)
- Approved for diabetes, obesity
- Under investigation for NASH

Compare efficacious doses head-to-head on histological endpoints in a rodent model of NASH (INT-767 10 mg/kg vs. Liraglutide 0.4 mg/kg; 8 weeks)

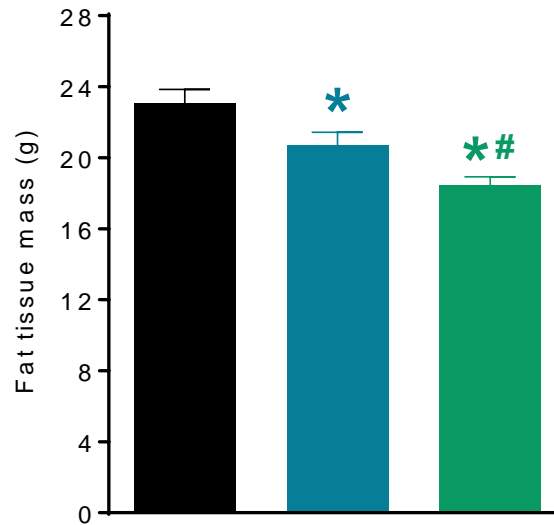
Body Weight, Adiposity and Food Intake



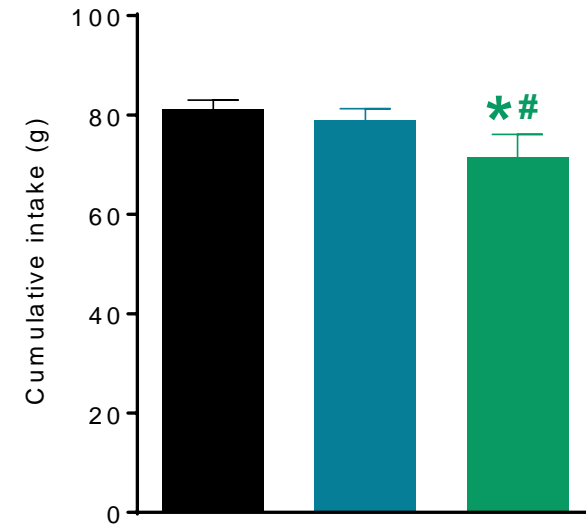
Body Weight



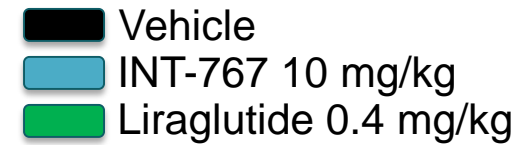
Fat Mass



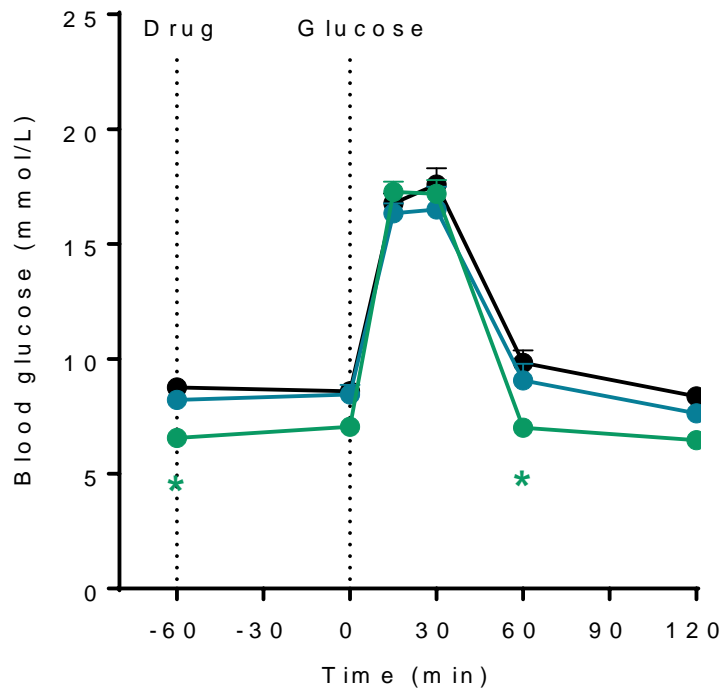
Food Intake



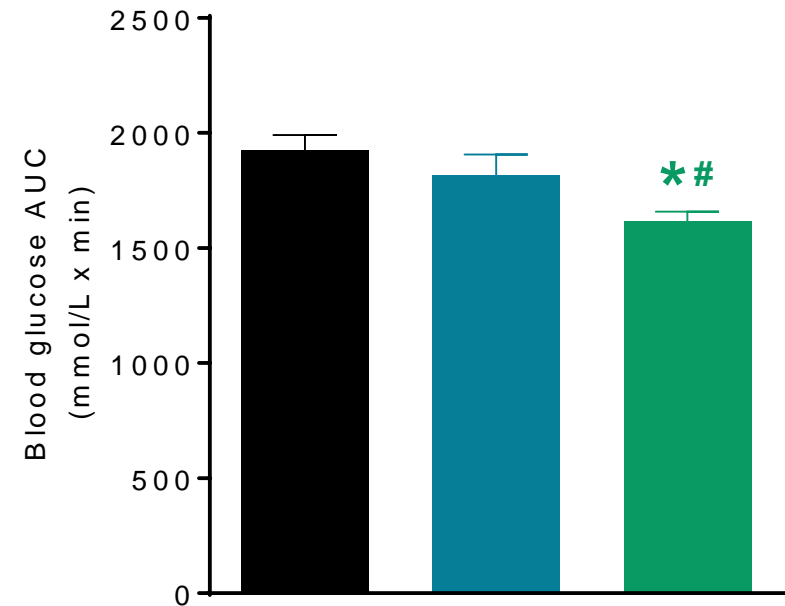
Glycemic Control



Oral Glucose Tolerance

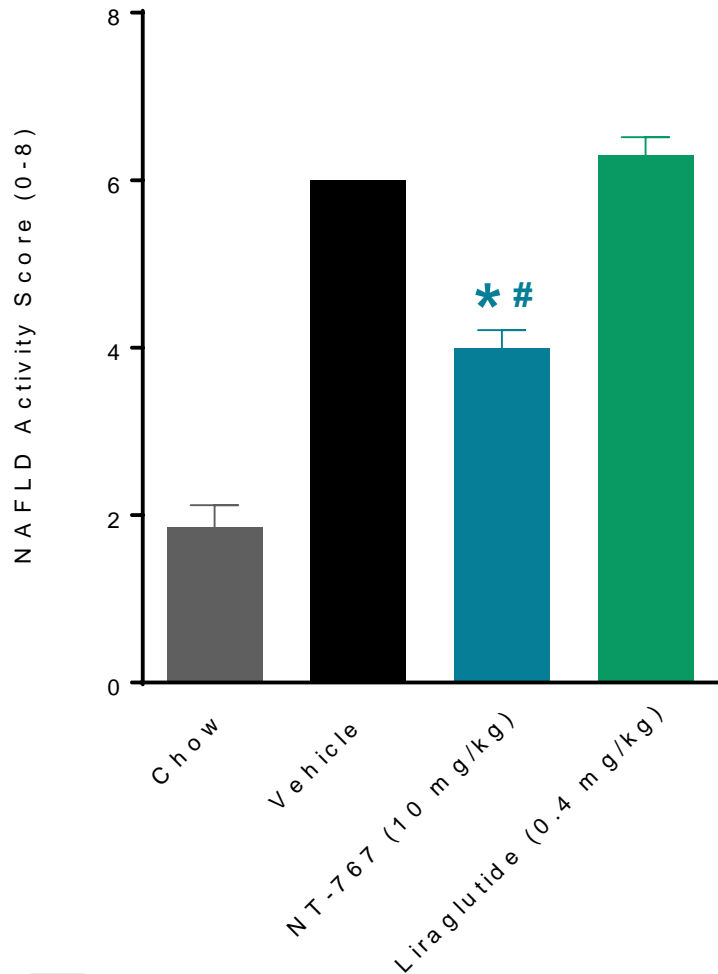


Area Under Curve

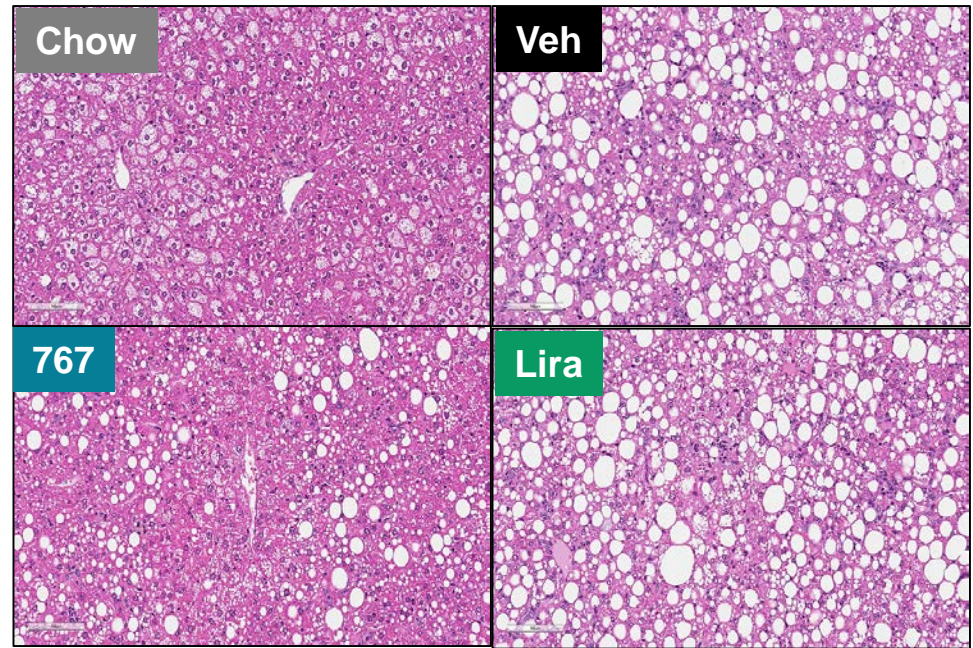


NAFLD Activity Score

NAFLD Activity Score

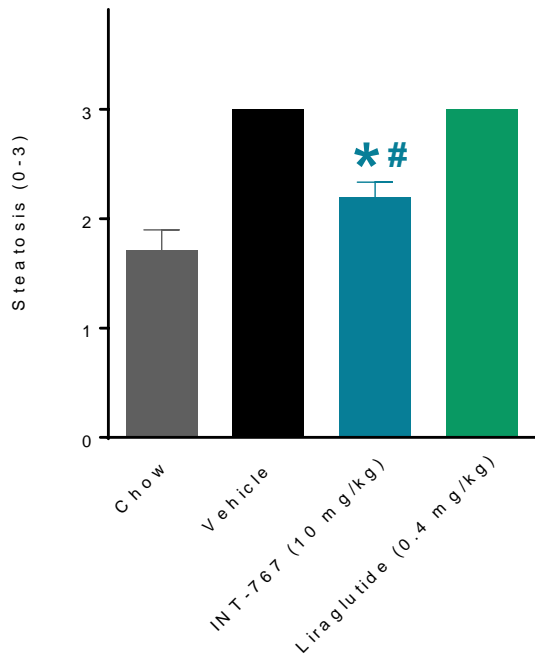


Representative H&E Stained Sections

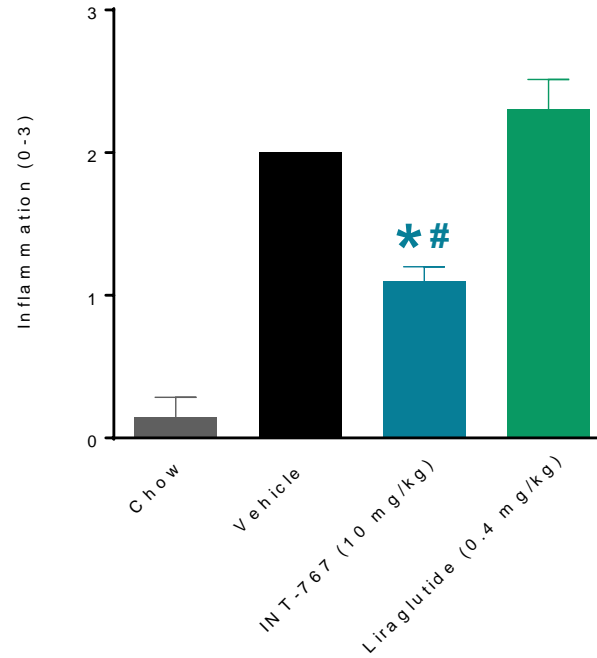


NAS Components

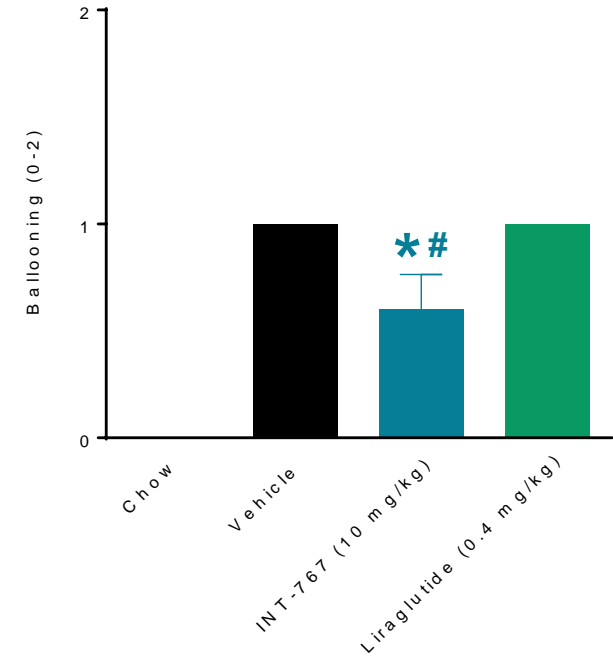
Steatosis



Inflammation

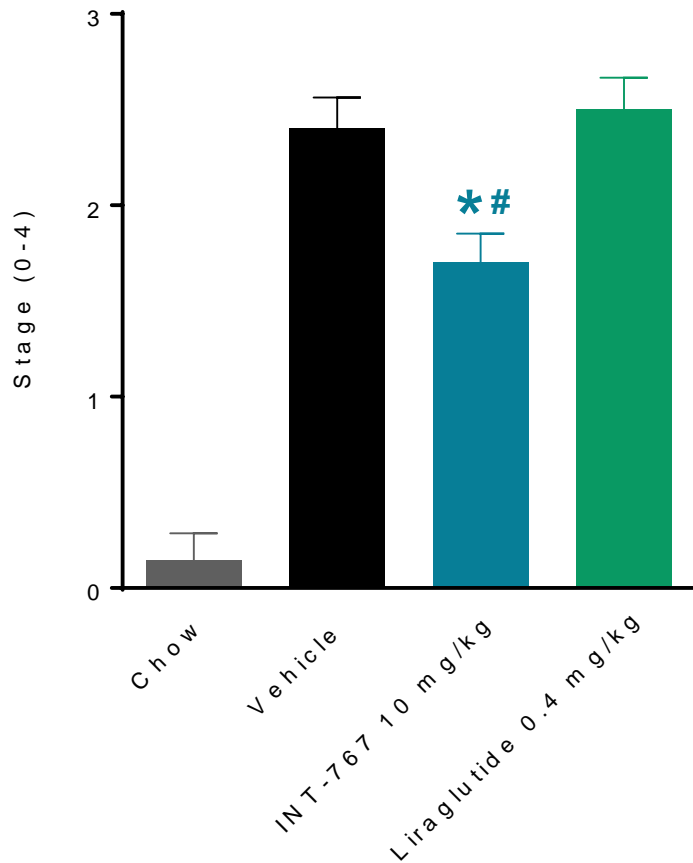


Ballooning

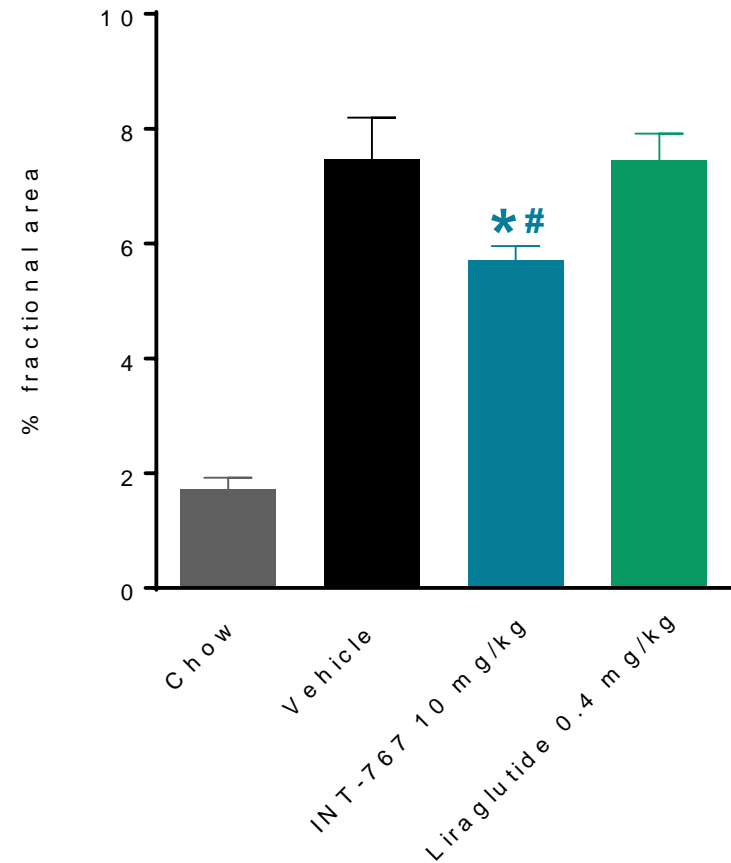


Fibrosis Scoring and Quantitation

Fibrosis Stage



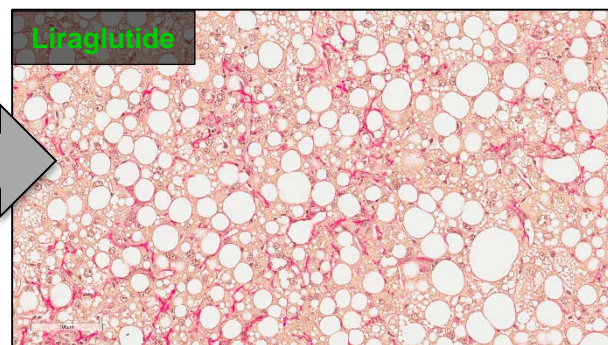
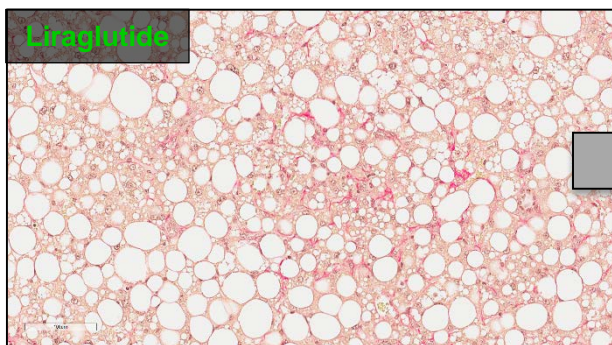
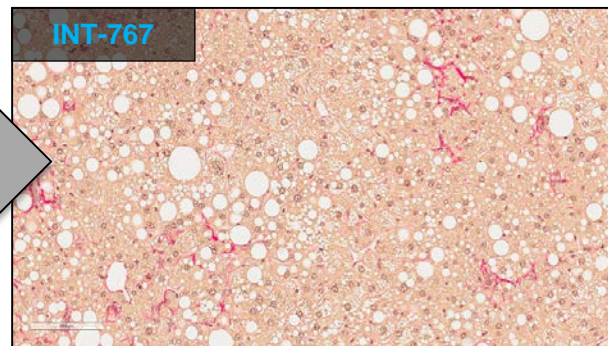
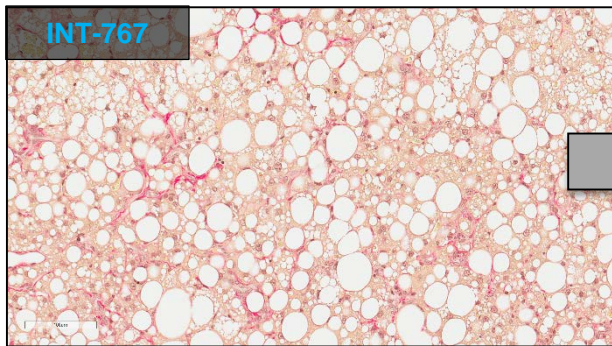
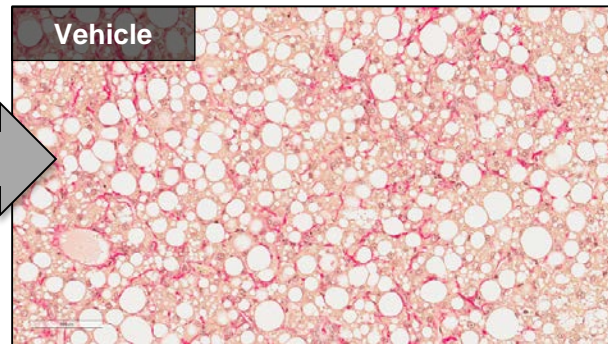
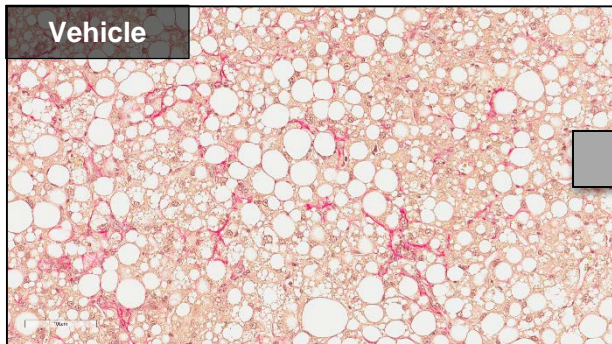
Fibrosis % Fractional Area



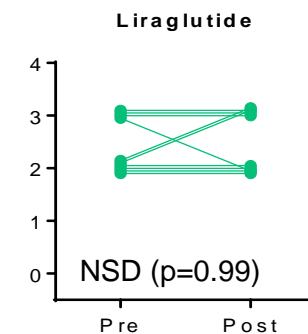
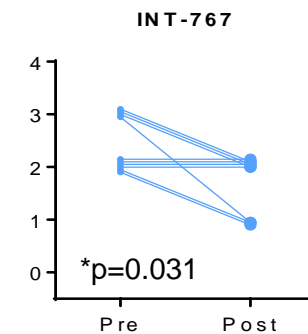
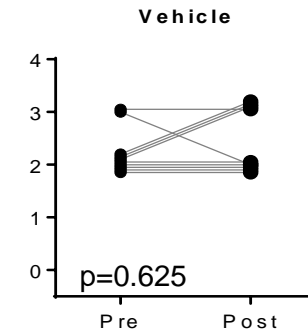
Fibrosis Stage: Pre- / Post-scores

Pre-Biopsy

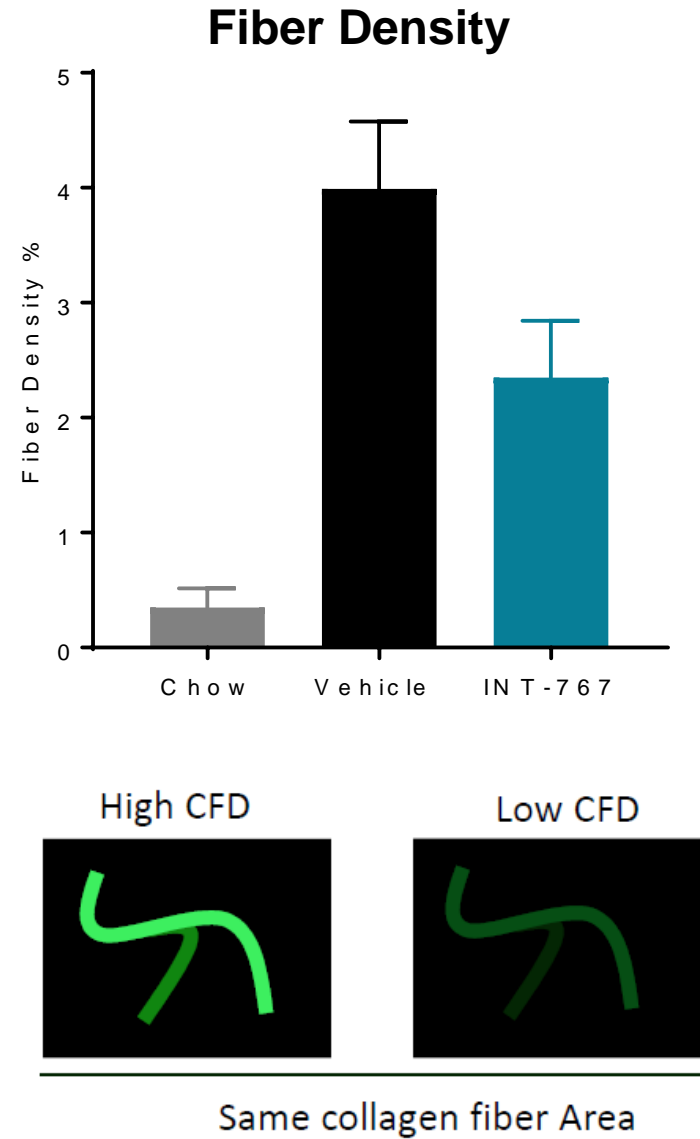
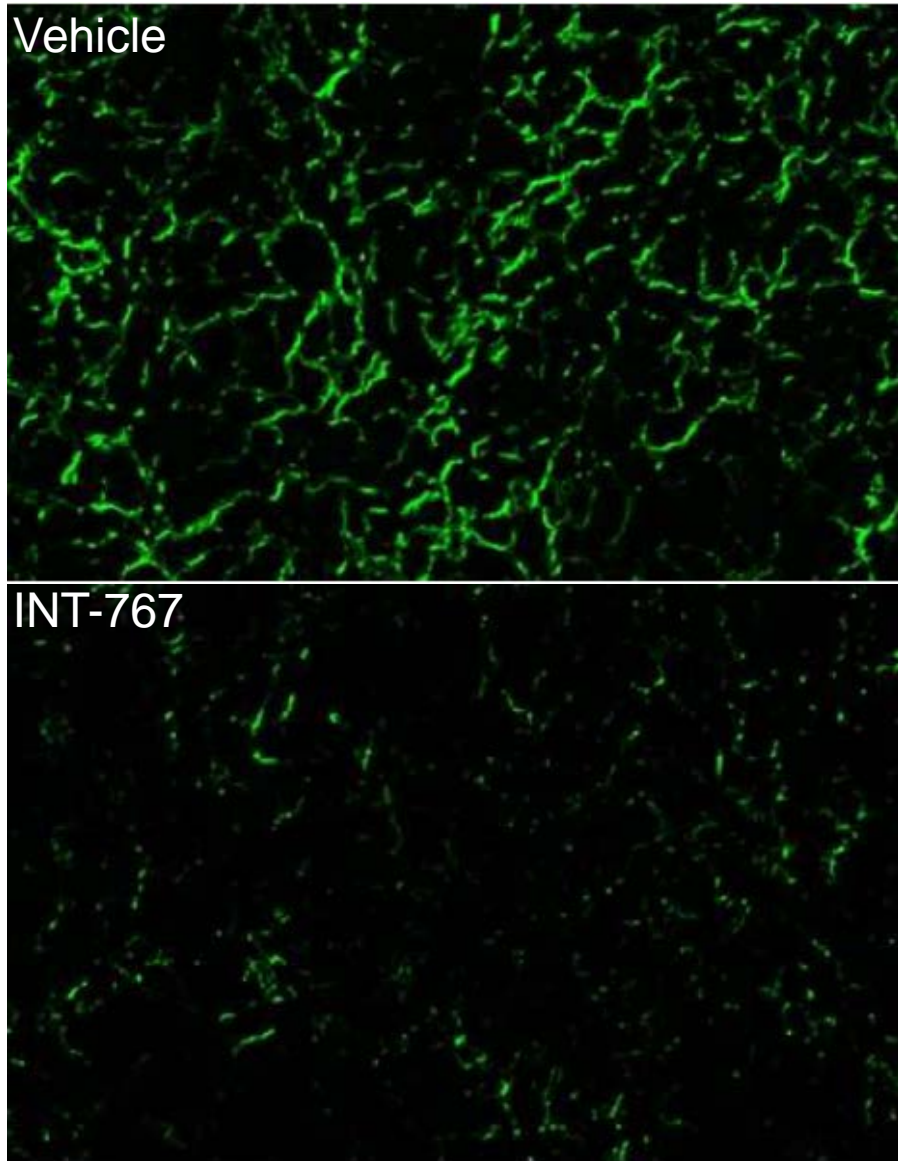
Post-Biopsy



Line Graphs



Detailed Analyses of Fibrosis

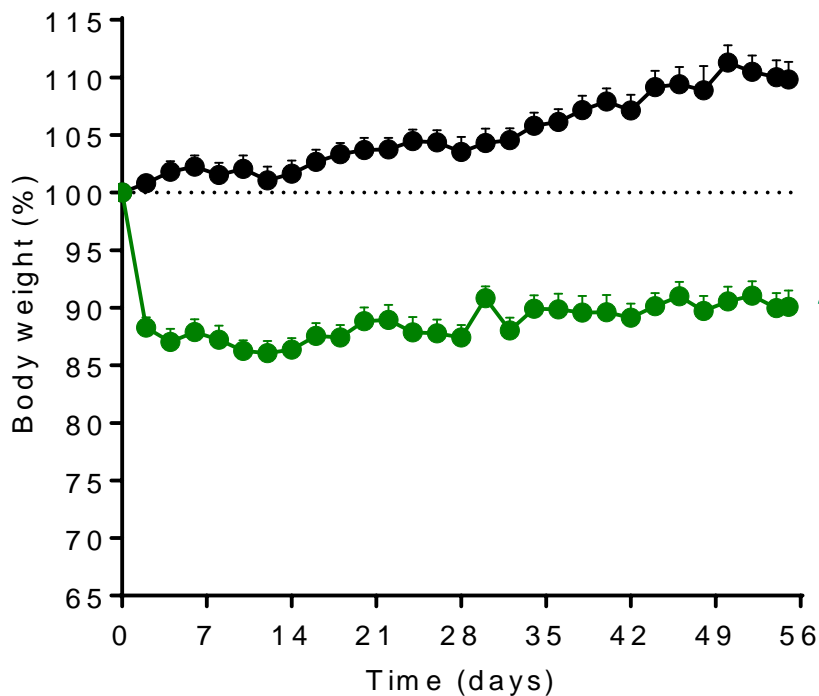


Liraglutide in the C57Bl6 AMLN NASH Model

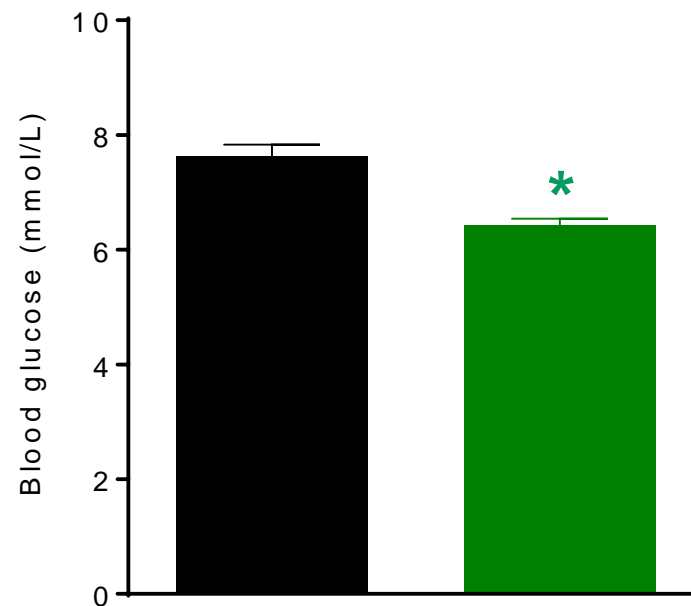
Body Weight and Glucose

Vehicle
Liraglutide 0.4 mg/kg

Body Weight

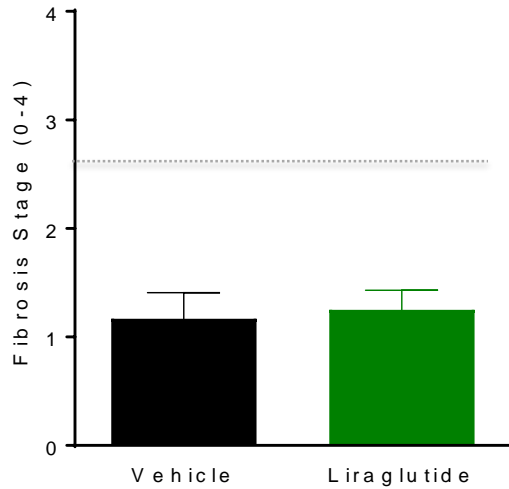


4 h Fasting Blood Glucose

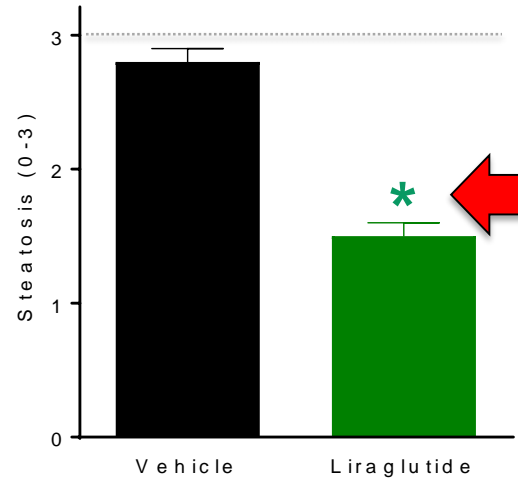


Liraglutide in the C57BI6 AMLN NASH Model Fibrosis and NAS

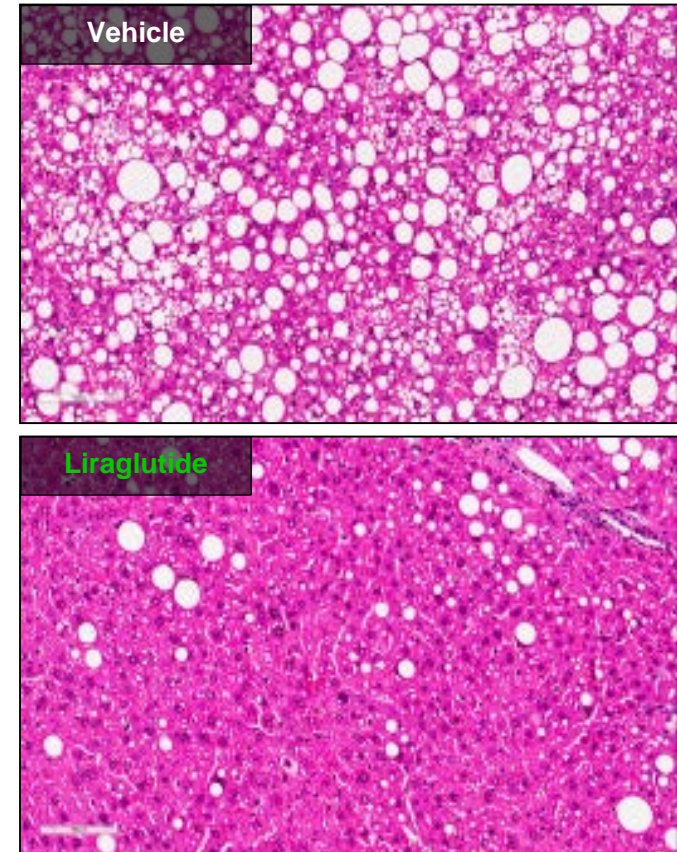
Fibrosis



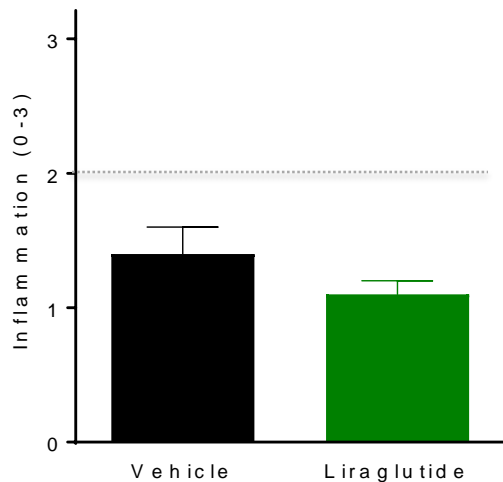
Steatosis



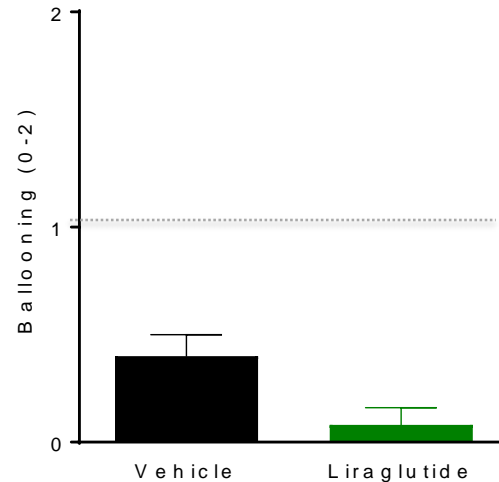
H&E Stained Sections



Inflammation



Ballooning



Summary and Conclusions

- INT-767 alleviated histological NASH in AMLN diet-fed *Lep^{ob/ob}* mice
 - ↓ Steatosis by 27%, inflammation by 45%, ballooning by 80%
 - ↓ Fibrosis score by 29% and percent fractional area by 24%
- Despite expected GLP-1R pharmacological effects to reduce body weight and glucose, liraglutide did not improve histological NASH in AMLN diet-fed *Lep^{ob/ob}* mice
- In a follow-up study in AMLN diet-fed C57Bl6 mice, Liraglutide improved NAS due to a reduction in steatosis (only)
- In models of AMLN diet-induced NASH, INT-767 does not require intact leptin signaling to improve NASH, whereas Liraglutide improved only steatosis, in a leptin-dependent manner

Acknowledgements

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