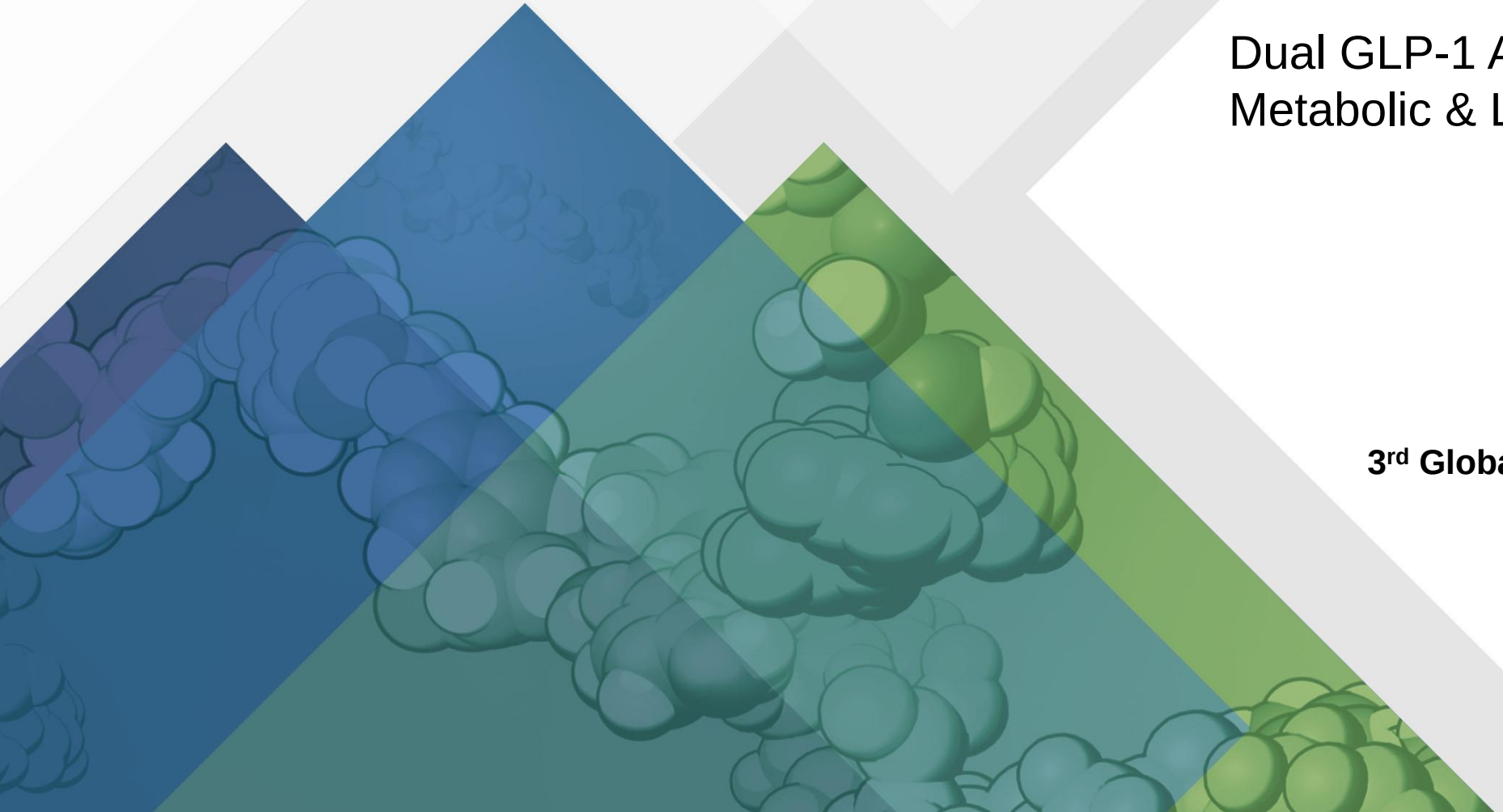

Dual GLP-1 Agonists in the Treatment Metabolic & Liver Dysfunction in NASH

M. Scott Harris, MD
Chief Medical Officer
Altimmune
Gaithersburg, MD USA

3rd Global NASH Conference 2020
London, UK
10-11 February 2020

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NASH and NAFLD

HEPATIC MANIFESTATIONS OF OBESITY AND METABOLIC SYNDROME

- NAFLD is present in up to **90% of obese patients**[1]
- **Up to 40% of NASH patients develop NAFLD** recurrence one year after liver transplant—the underlying metabolic disease is still present[2]
- The **treatment of obesity** is the cornerstone of treating not only NASH but the principal morbidities of NASH (cardiovascular, malignancy)[1,3]
- Drugs in development should target the **weight loss range achieved by bariatric surgery**[4]

[1]Glass LM, Fed Pract 2019; [2]Dureja, P, Transplantation 2011; [3]Perazzo H, Liver Int 2017; [4]Armstrong M, Vantage December 14, 2018

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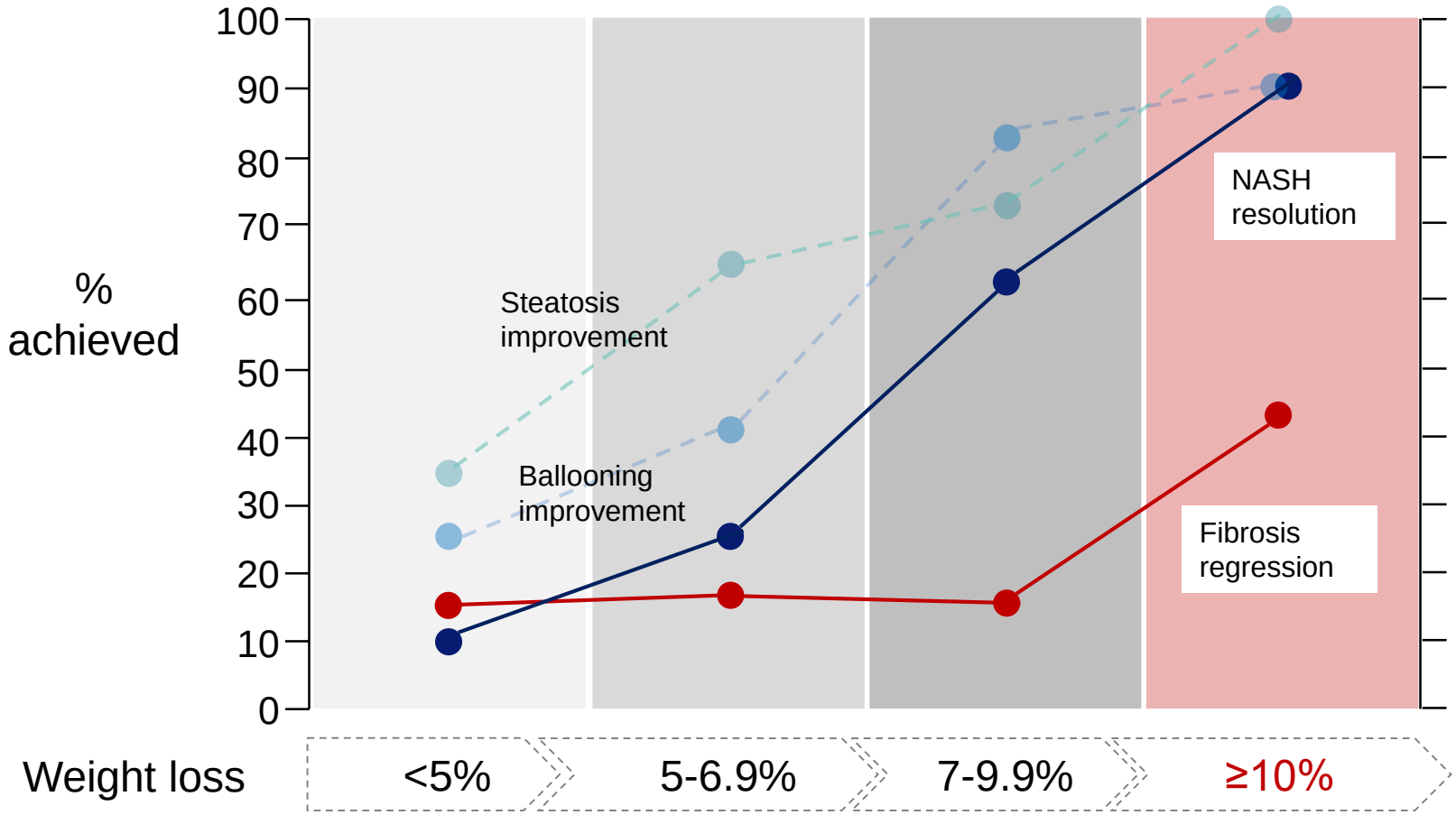
Substantial Body Weight Loss Blunts NASH Progression[1]

10% OR MORE WEIGHT LOSS MUST BE ACHIEVED



[1]*Promrat et al Hepatology 2010; Glass et al Dig Dis Sci 2015; Vilar-Gomez et al Gastroenterology 2015; Marchesini et al Hepatology 2016; Koutowkidis et al JAMA Intern Med 2019*

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Snapshot of Compounds in Advanced NASH Development

MOST AGENTS FAIL TO ACHIEVE MEANINGFUL LEVELS OF WEIGHT LOSS

Agent	Author (year)	Mechanism	Weight Loss (%)
Obeticholic acid	Younossi, ZM 2019[1]	FXR agonist	~2%
Resmetirom	Harrison, SA 2018[2]	THRβ agonist	NC
Aldafermin (3mg)†	Harrison, SA 2019[3]	FGF19 agonist	1.3%
Pegbelfermin (10 mg)††	Sanyal, A[4] 2018	FGF21 agonist	2.2%
Firsocostat	Lawitz, EJ 2018[5]	ACC inhibitor	NC
Elafibranor	Ratziu, V 2016[6]	PPARα/δ agonist	NC

† No information has been made public on 1mg dose

†† Gain of 0.6% on 20mg dose

NC, no change

[1]Younossi, YM, et al. (2019) Lancet 394: 2184-96; [2]Harrison, SA, et al. Lancet 394: 2012-24; [3] Harrison, SA, et al. (2019) Lancet 391:1174-85; [4]Sanyal, A, et al. (2018) Lancet 392:2705-17; [5]Lawitz, EJ, et al. (2018) Clin Gastroenterol Hepatol 16:1983-91; [6]Ratziu, V, et al. (2016) Gastroenterol 150: 1147-59

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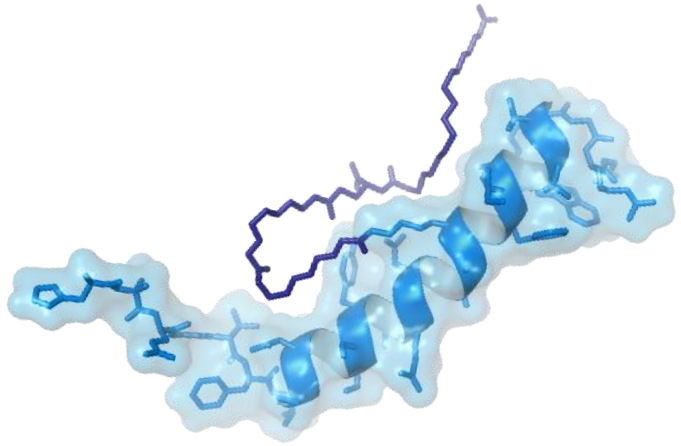
Slide courtesy of Dr. Stephen Harrison

NASH
GLP-1 ANALOGUES HAVE MULTIPLE BENEFICIAL EFFECTS

NASH
- **Inflammation[3] ↓**
- **Body weight[8] ↓**
- **Lipids[*4,5] ↓**
- **Glucose[1] ↓**



CV disease
- **Inflammation[3] ↓**
- **Lipids[*4,5] ↓**
- **Systolic blood pressure ↓**
- **Heart rate[6] ↑**

Obesity
- **Energy intake[7] ↓**
- **Appetite[8] ↓**
- **Body weight[8] ↓**

Kidney disease
- **Inflammation[3] ↓**
- **Systolic blood pressure[6] ↓**

Diabetes
- **Insulin[1] ↑**
- **β-cell function[1] ↑**
- **Glucagon[1] ↓**
- **Gastric emptying[2] ↓**

[*]Fasting and post-prandial lipids.

CV, cardiovascular; GLP-1, glucagon-like peptide-1; NASH, non-alcoholic steatohepatitis.

1. Campbell JE and Drucker DJ. *Cell Metab* 2013;17:819–37; 2. Tong J and D'Alessio D. *Diabetes* 2014;63:407–9; 3. Hogan AE, *et al. Diabetologia* 2014;57:781–4; 4. Hermansen K, *et al. Diabetes Obes Metab* 2013;15:1040–8; 5. Ahrén B, *et al. Lancet Diabetes Endocrinol* 2017;5:341–54; 6. Ryan D and Acosta A. *Obesity* 2015;23:1119–29; 7. Bagger JI, *et al. J Clin Endocrinol Metab* 2015;100:4541–52; 8. Flint A, *et al. J Clin Invest* 1998;101:515–20.

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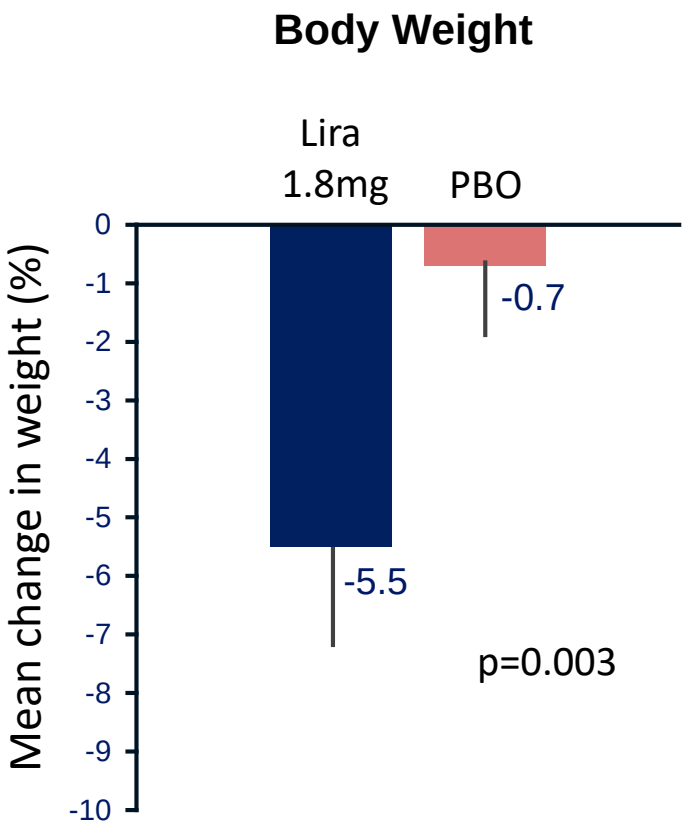
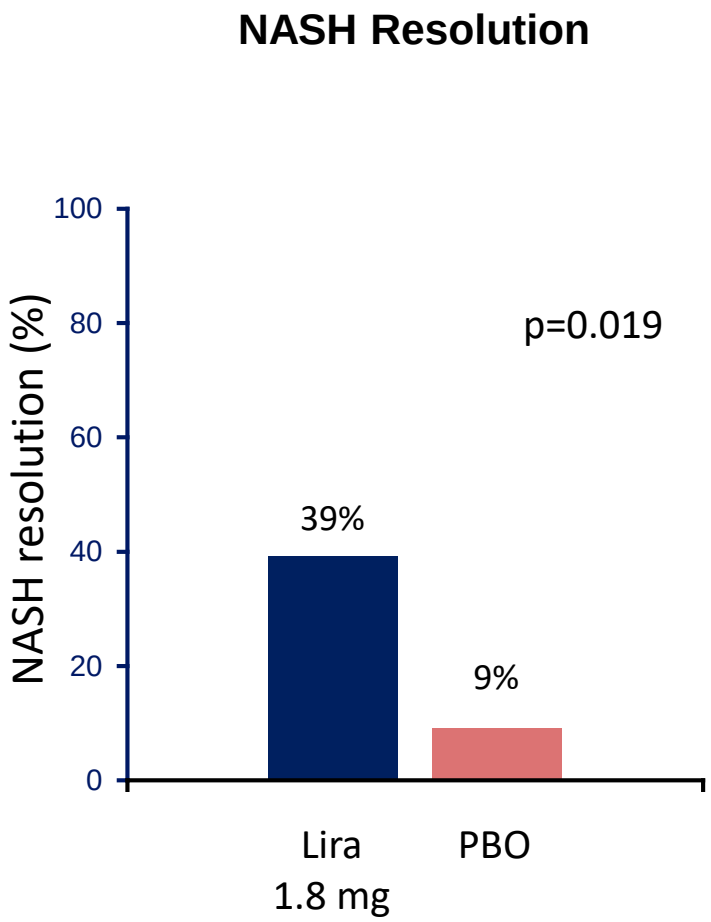
NASH Trial (LEAN)

LIRAGLUTIDE DAILY (48 WEEKS)—WEIGHT LOSS AND NASH RESOLUTION





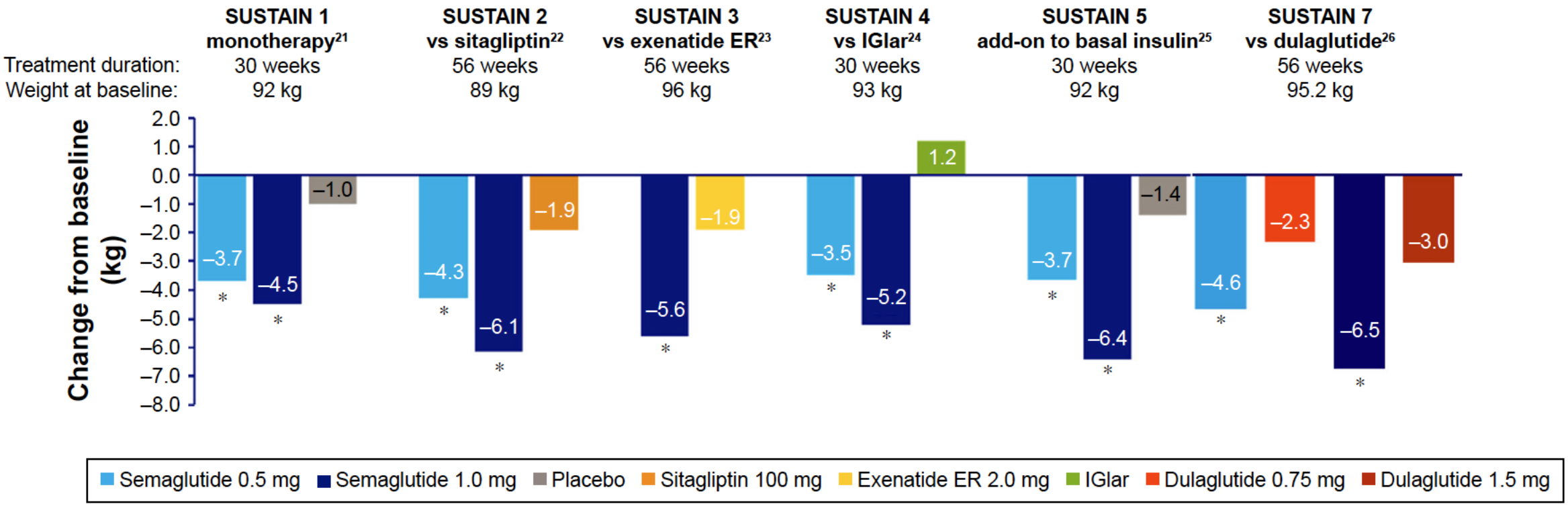
PBO, placebo

Armstrong MJ, Lancet 2016;387:679–90; Armstrong MJ, et al. BMJ Open 2013;3:e003995.

6

Semaglutide SUSTAIN Trials (0.5 – 1.0 mg/week)

WEIGHT LOSS OF ONLY 5% TO 7% AFTER 30 TO 56 WEEKS TREATMENT



ALT, alanine aminotransferase; PBO, placebo

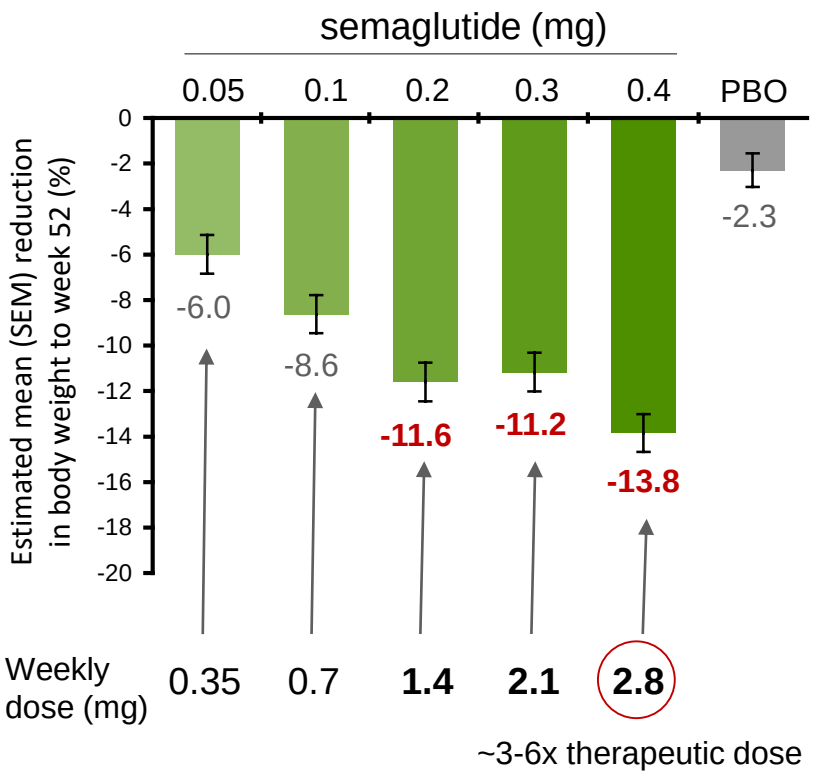
Gomez-Peratta F, et al, Drug Design, Development and Therapy 2019:13 731–738

7

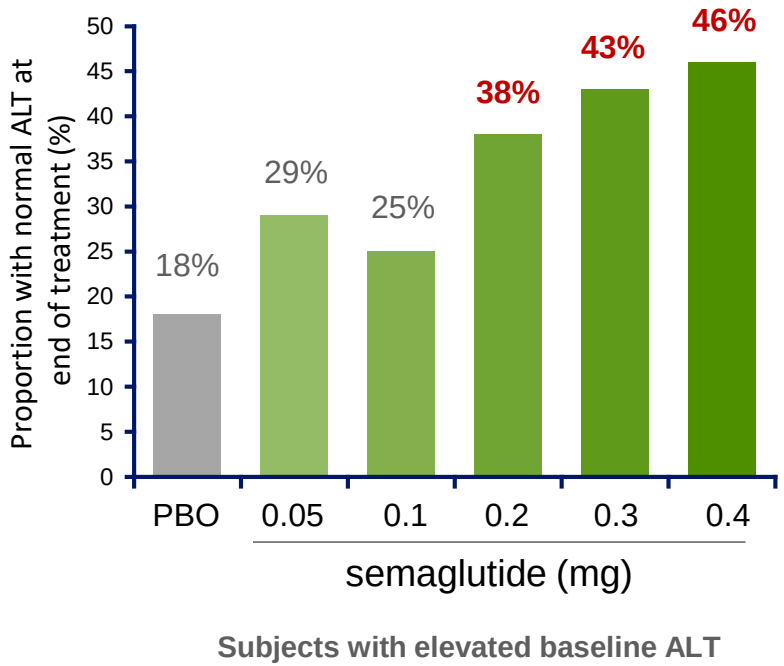
Semaglutide Obesity Trial (0.05 to 0.4 mg/day)

DRIVING WEIGHT LOSS AT THE EXPENSE OF GI SIDE EFFECTS

Body Weight

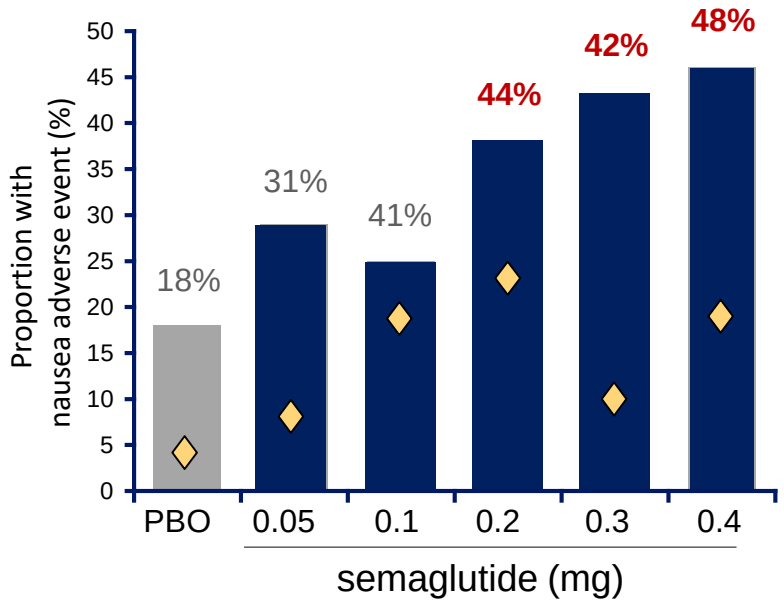


ALT



Subjects with elevated baseline ALT

Nausea /Vomiting



ALT, alanine aminotransferase;; PBO, placebo

O'Neil PM, et al. Lancet 2018;392:637–49.

8

GLP-1/Glucagon Receptor Dual Agonists

OPTIMIZED FOR NASH AND WEIGHT LOSS

GLP-1

blood glucose

appetite

inflammation

Indirect effects on liver

GLUCAGON

energy expenditure

adipose browning

lipolysis/ gluconeogenesis

mobilization of liver fat

Direct effects on liver

SIGNIFICANT REDUCTIONS IN

body weight

liver fat/cholesterol, inflammation, resulting fibrosis

blood glucose

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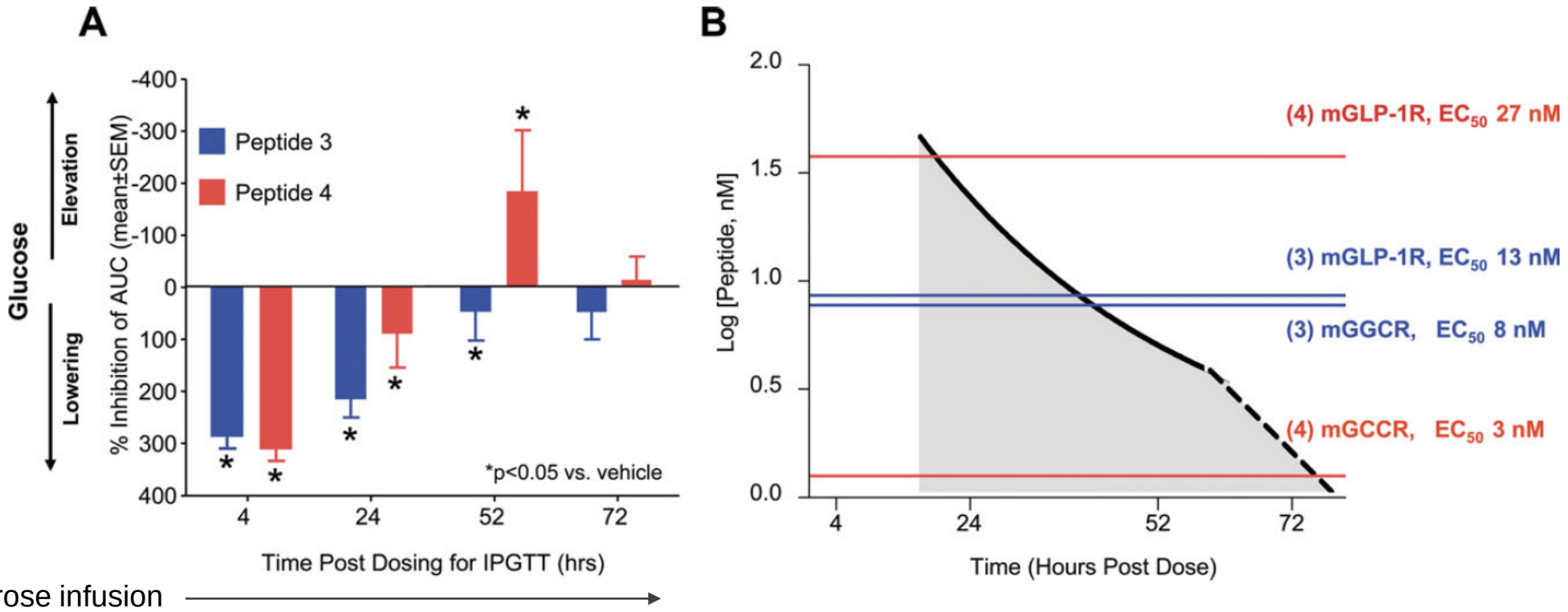
Consequences of Dual Agonism Imbalance

BIASED LIGAND RETAINS EFFECTS ON ONLY ONE RECEPTOR

Glucose concentration over dosing interval

Plasma exposure over dosing interval



IV dextrose infusion →

Day JA, et al. Peptide Science 2012;98:443-50

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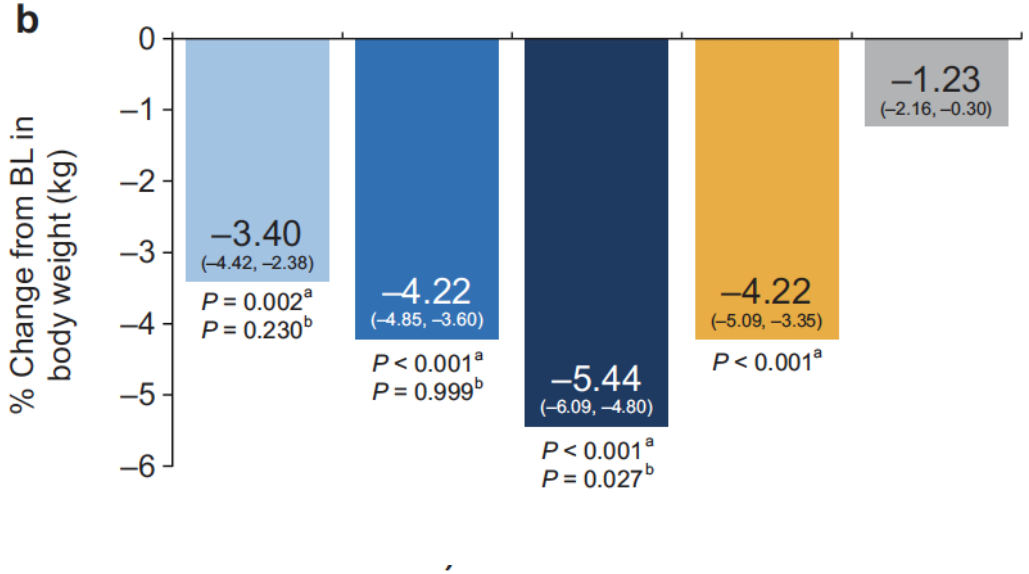
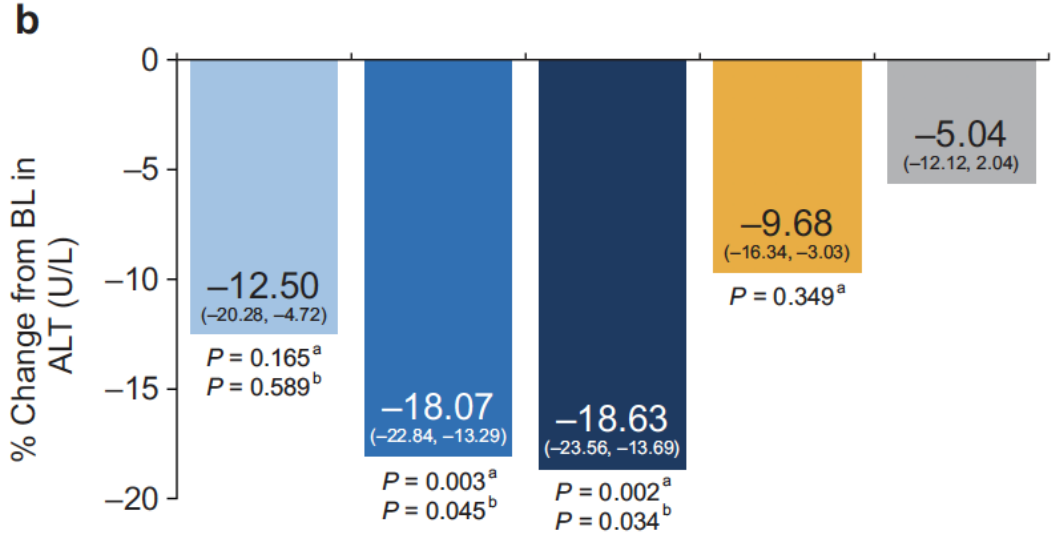
Cotadutide—5:1 GLP-1R/ GCGR Ratio

GREATER REDUCTION IN ALT AT SIMILAR LEVEL OF WEIGHT LOSS AS LIRAGLUTIDE

Loss of Body Weight (26 weeks)



Reduction in ALT (26 weeks)



Cotadutide 100 µg Cotadutide 200 µg Cotadutide 300 µg Liraglutide 1.8 mg Placebo

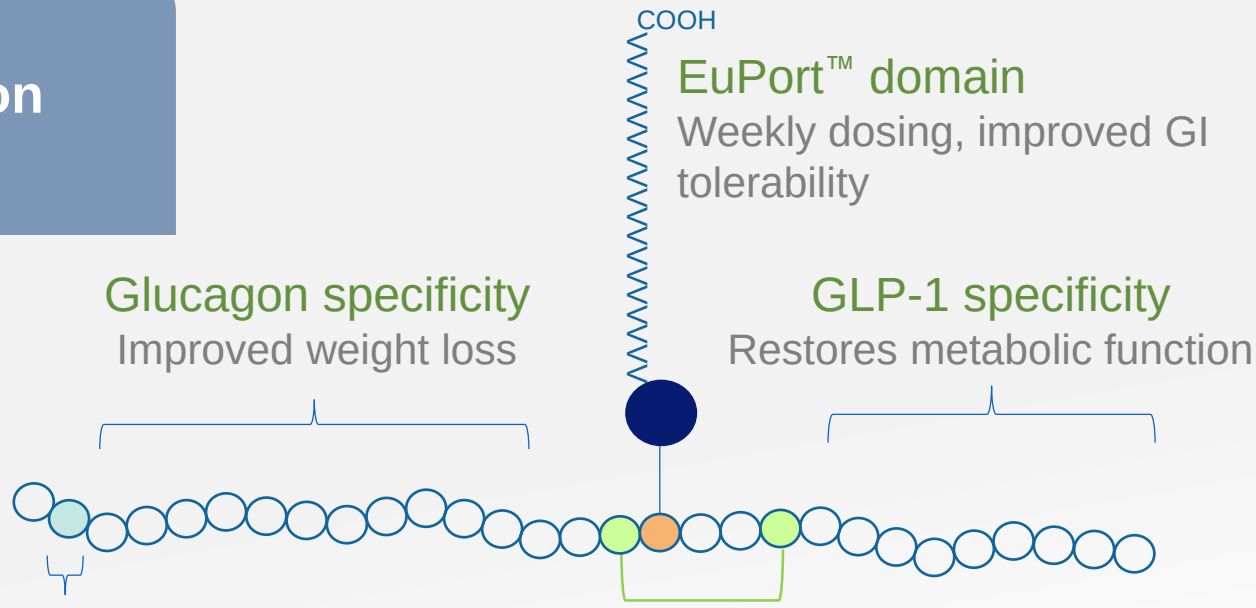
Nahra R et al, AASLD 2019

ALT-801

STRUCTURE IS KEY TO DIFFERENTIATION

Proprietary EuPort™ domain provides prolonged $t_{1/2}$ and reduced C_{max}

Balanced GLP-1:Glucagon Agonism



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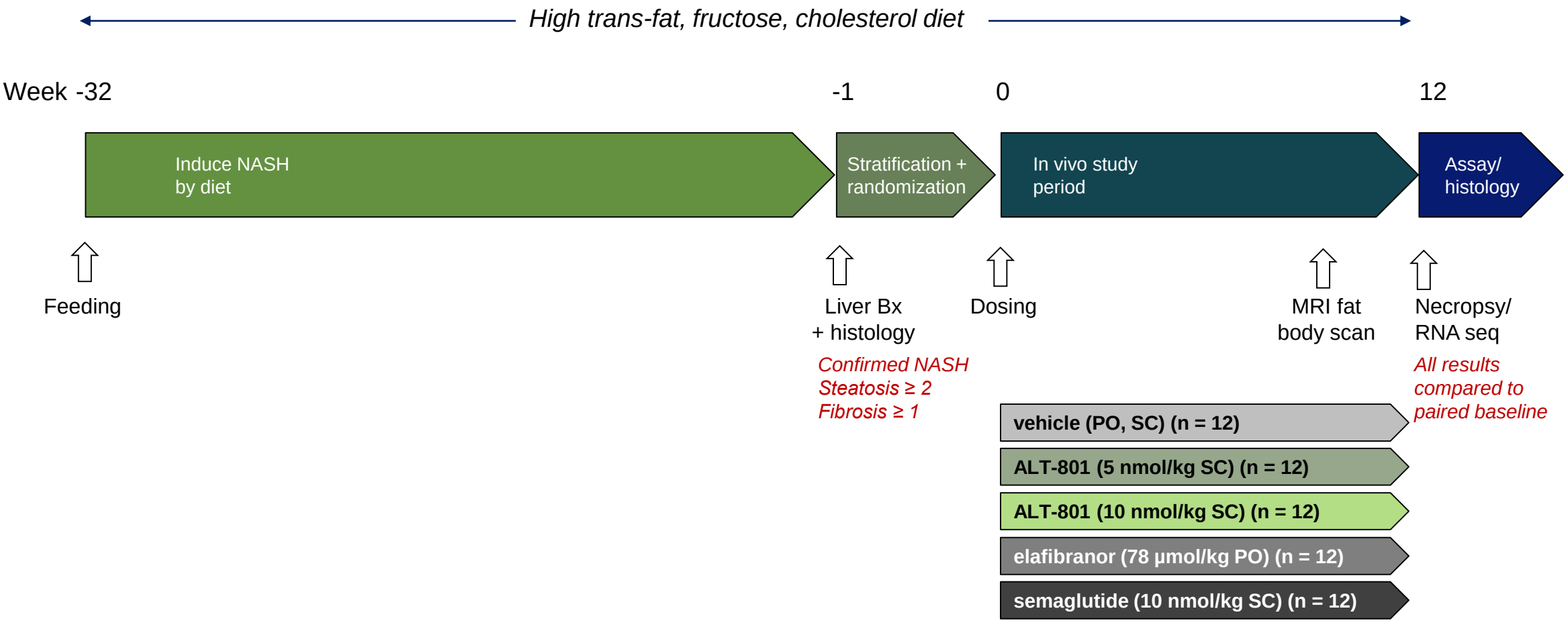
ALT-801
GUBRA AMYLIN NASH MODEL IN MALE C57BL/6J MICE



Hansen, HH, et al. (2017) Drug Disc Today 22 (11): 1707-18

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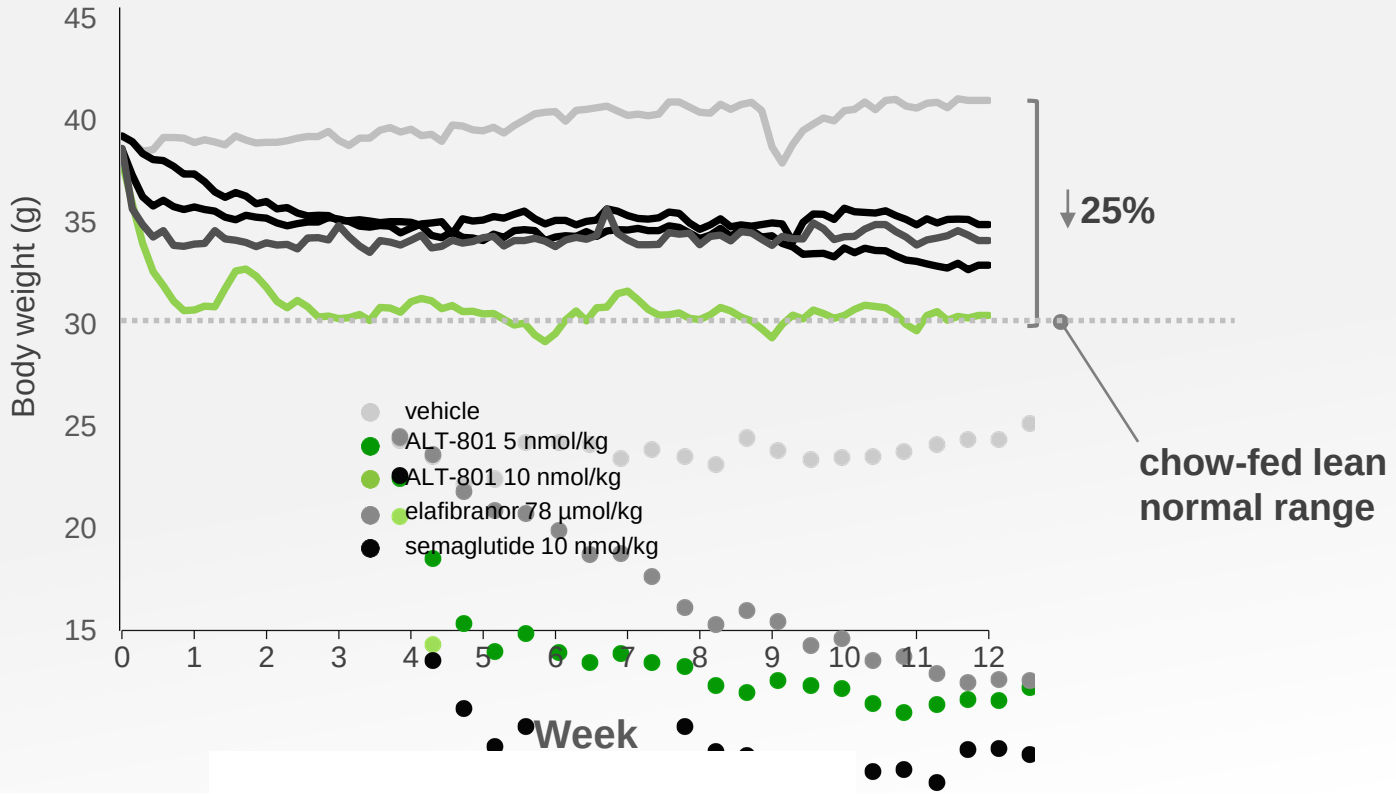
ALT-801

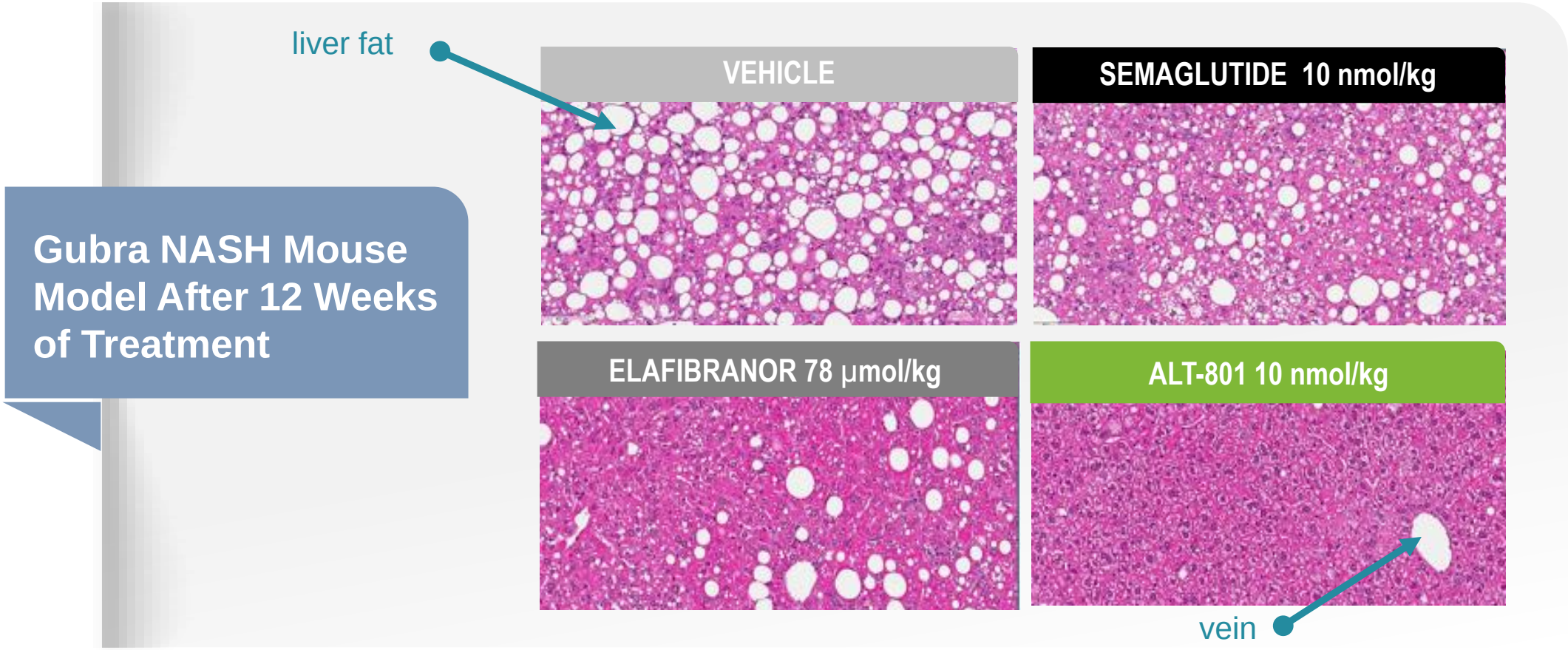
BODY WEIGHT RETURNED TO CHOW-FED LEAN NORMAL RANGE

Gubra NASH Mouse Model After 12 Weeks of Treatment



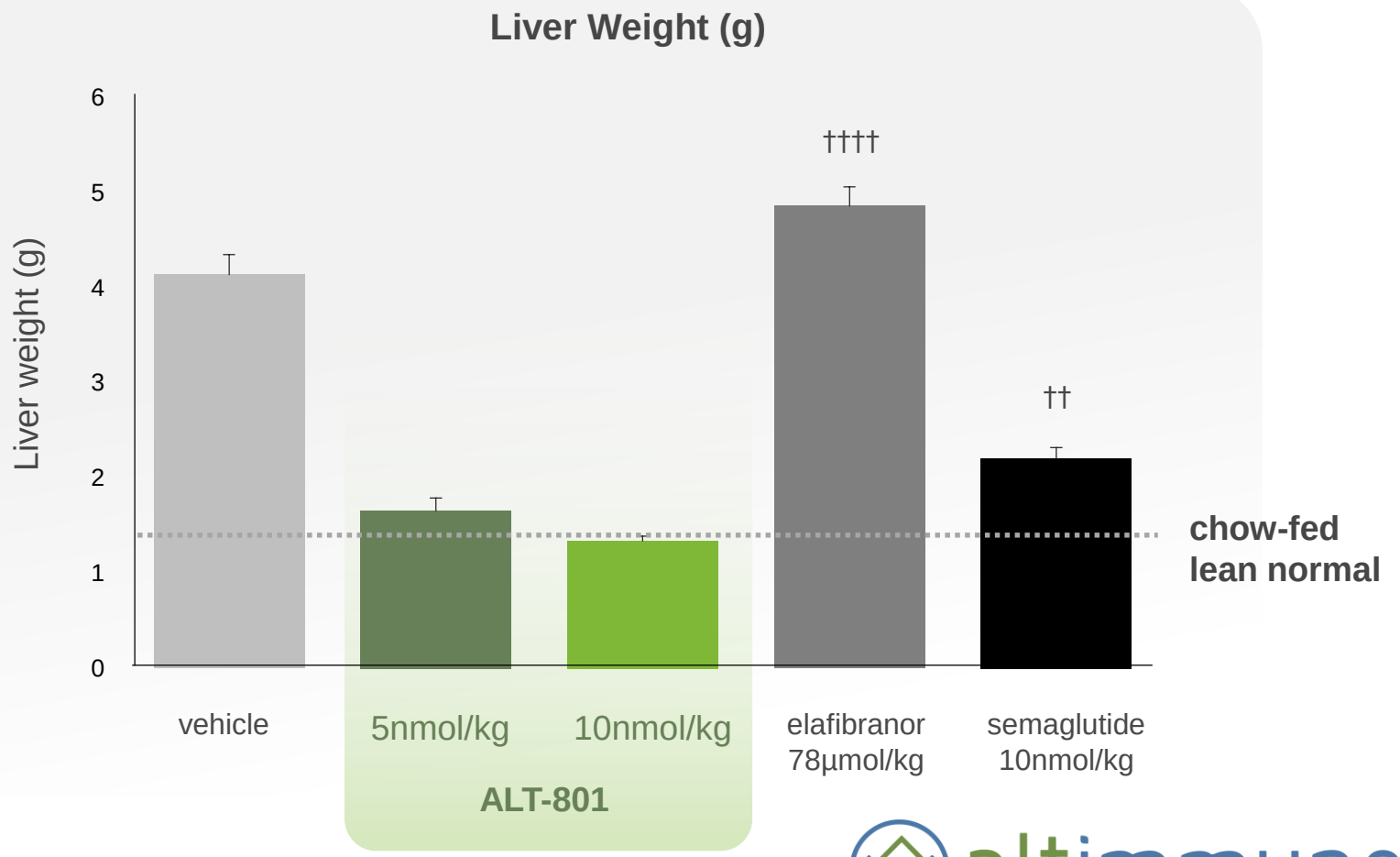
ALT-801
REDUCED LIVER FAT TO NEAR NORMAL HISTOLOGY

Gubra NASH Mouse Model After 12 Weeks of Treatment



ALT-801
LIVER WEIGHT NORMALIZED

Gubra NASH Mouse Model After 12 Weeks of Treatment



Mean (SE), 1-way ANOVA with Dunnett's adjustment for multiplicity
†† p < .01, ††† p < .001, ††††, p < .0001 vs. **ALT-801** 10 nmol/kg (n=11-12)

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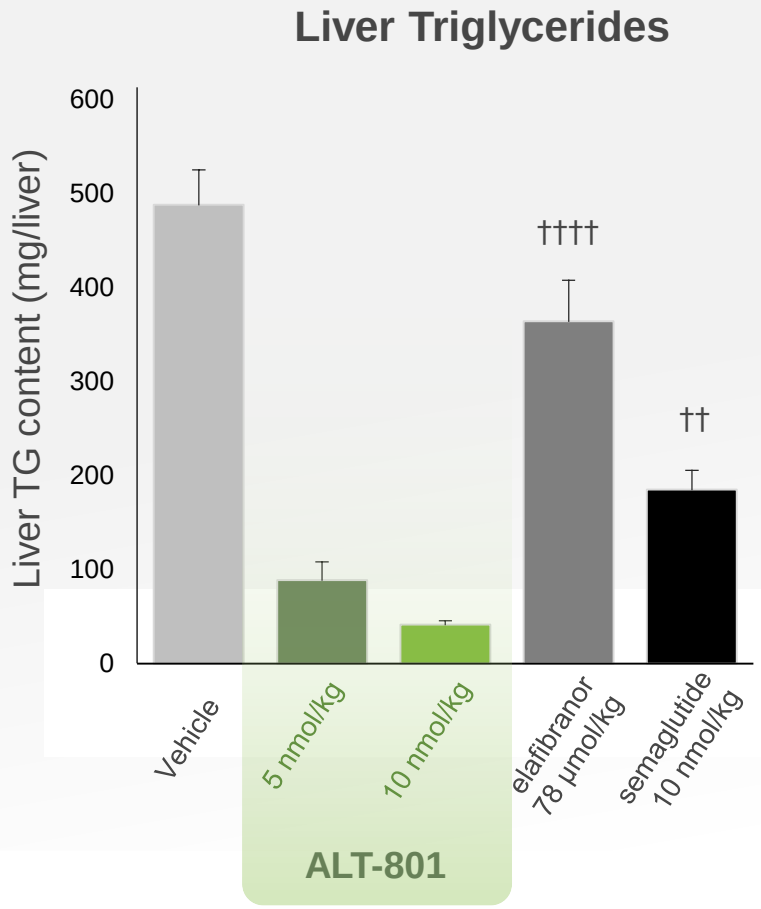
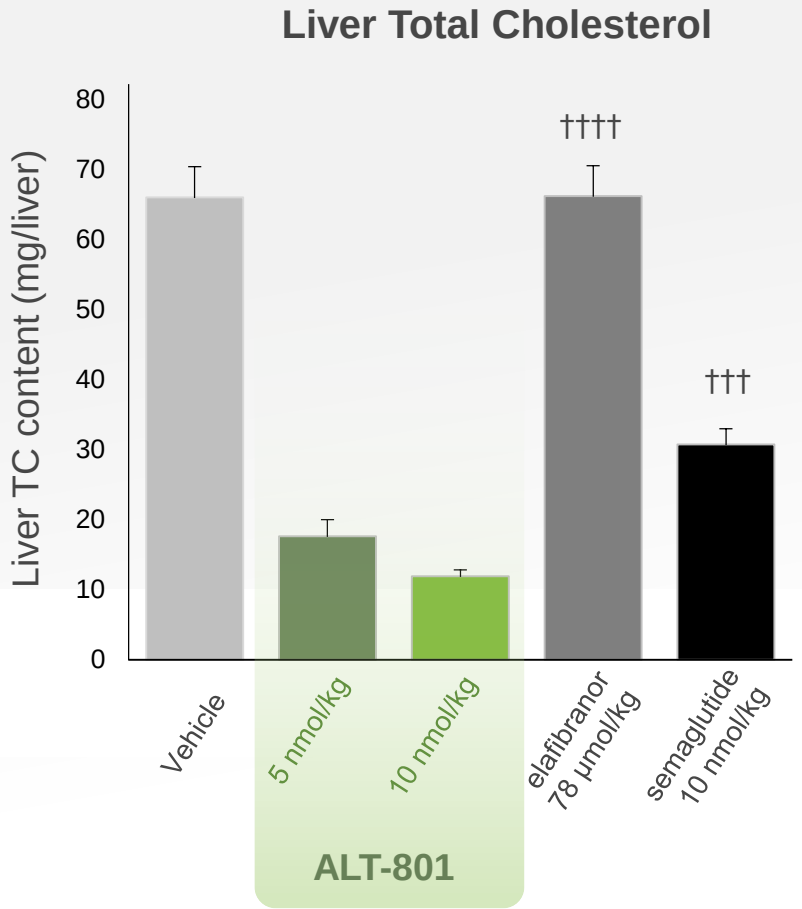
ALT-801

LIVER TRIGLYCERIDES (TG) AND TOTAL CHOLESTEROL (TC) NORMALIZED

Gubra NASH Mouse Model After 12 Weeks of Treatment





Mean (SE), 1-way ANOVA with Dunnett's adjustment for multiplicity
†† p < .01, ††† p < .001, ††††, p < .0001 vs. **ALT-801** 10 nmol/kg (n=11-12)

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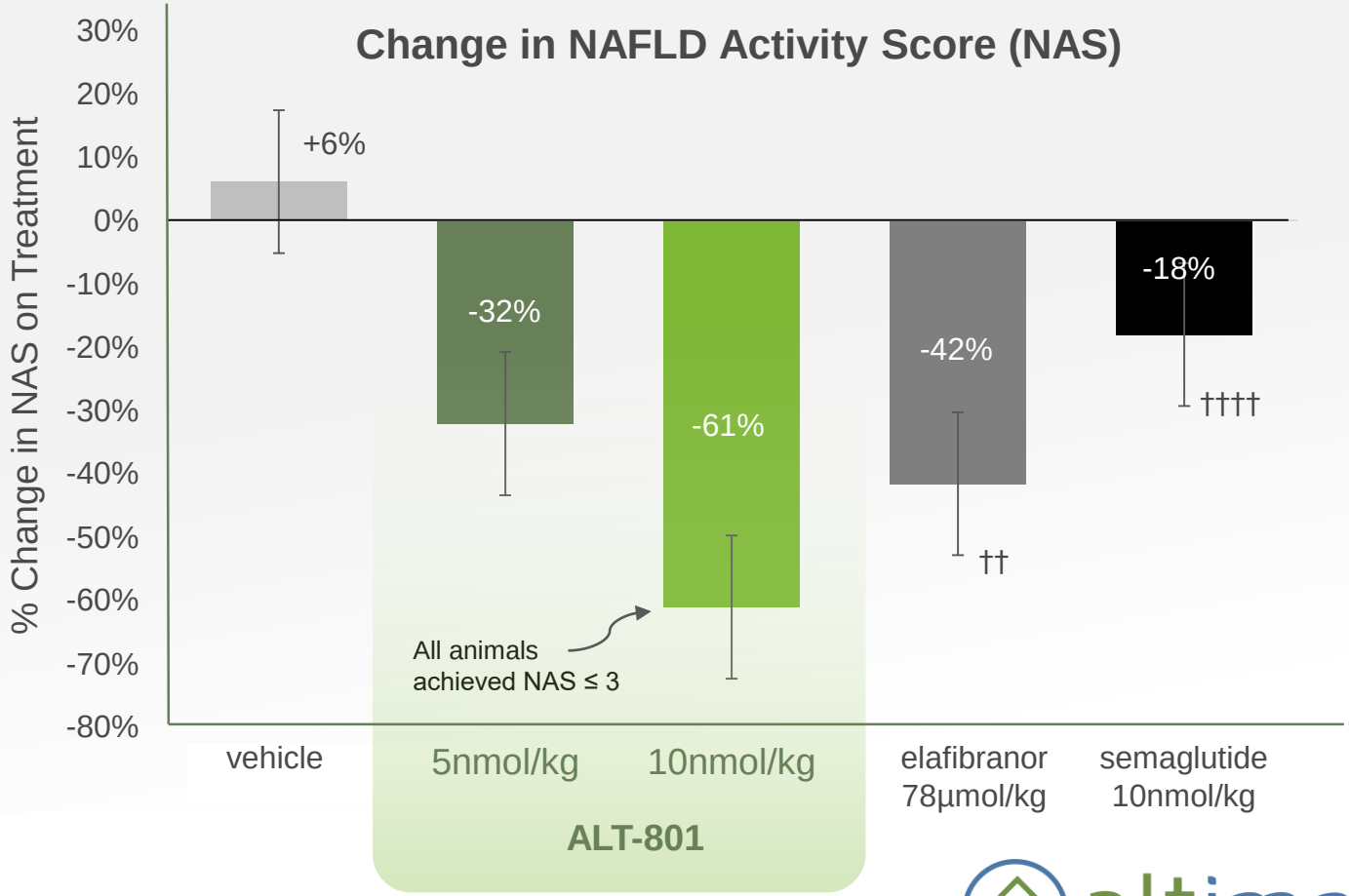
ALT-801
GREATER REDUCTION IN NAFLD ACTIVITY SCORE (NAS)

Gubra NASH Mouse Model After 12 Weeks of Treatment



Mean (SE), 1-way ANOVA with Dunnett's adjustment for multiplicity
†† p < .01, ††† p < .001, ††††, p < .0001 vs. ALT-801 10 nmol/kg (n=11-12)

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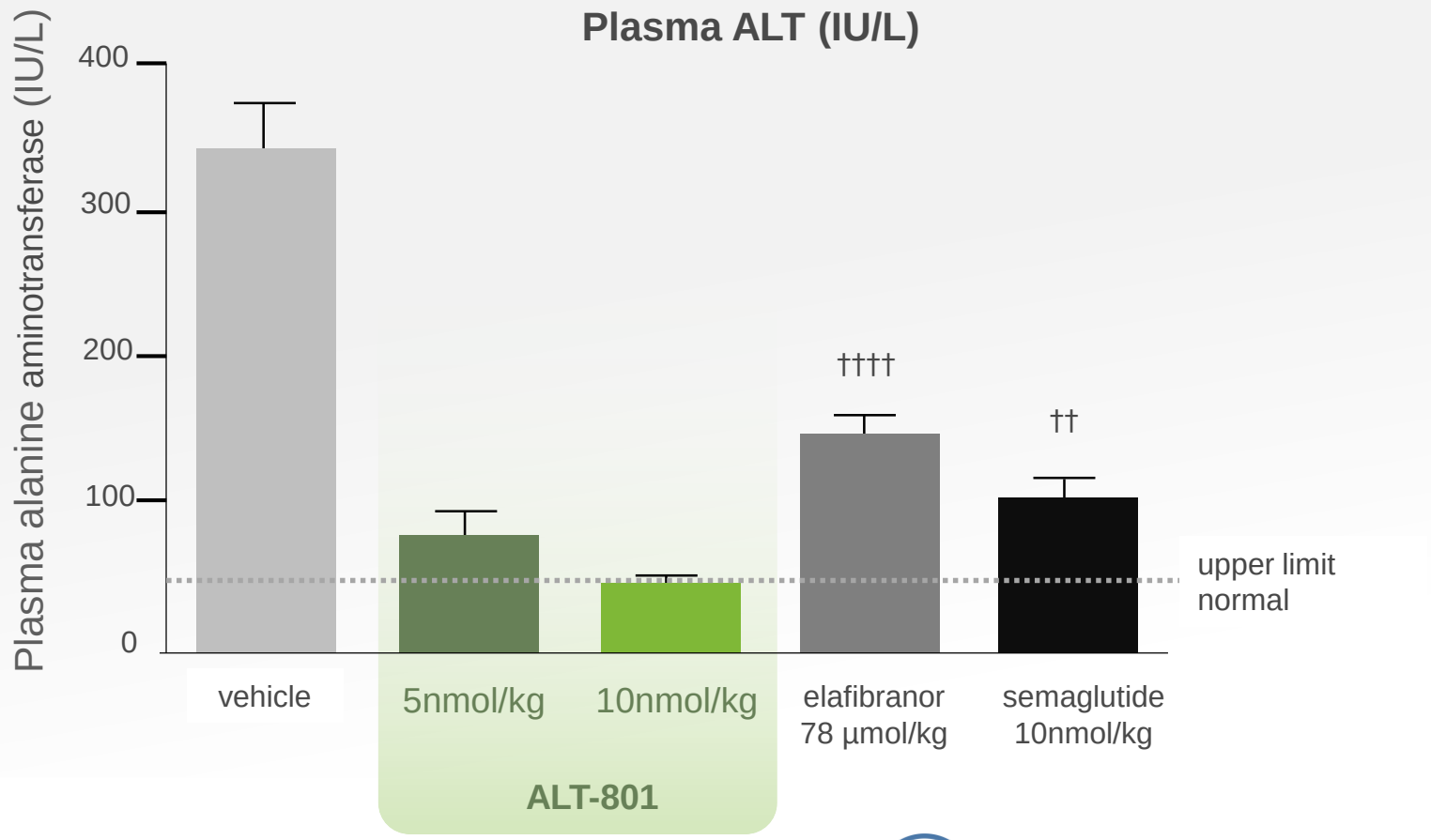
ALT-801
PLASMA ALT NORMALIZED

Gubra NASH Mouse Model After 12 Weeks of Treatment



Mean (SE), 1-way ANOVA with Dunnett's adjustment for multiplicity
†† p < .01, ††† p < .001, ††††, p < .0001 vs. **ALT-801** 10 nmol/kg (n=11-12)

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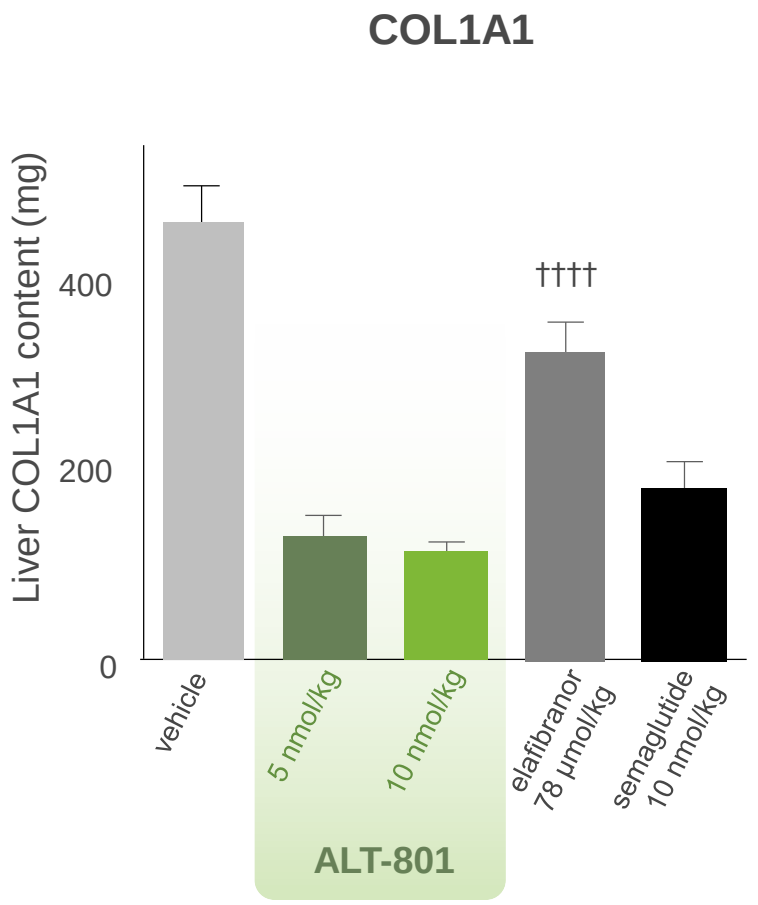
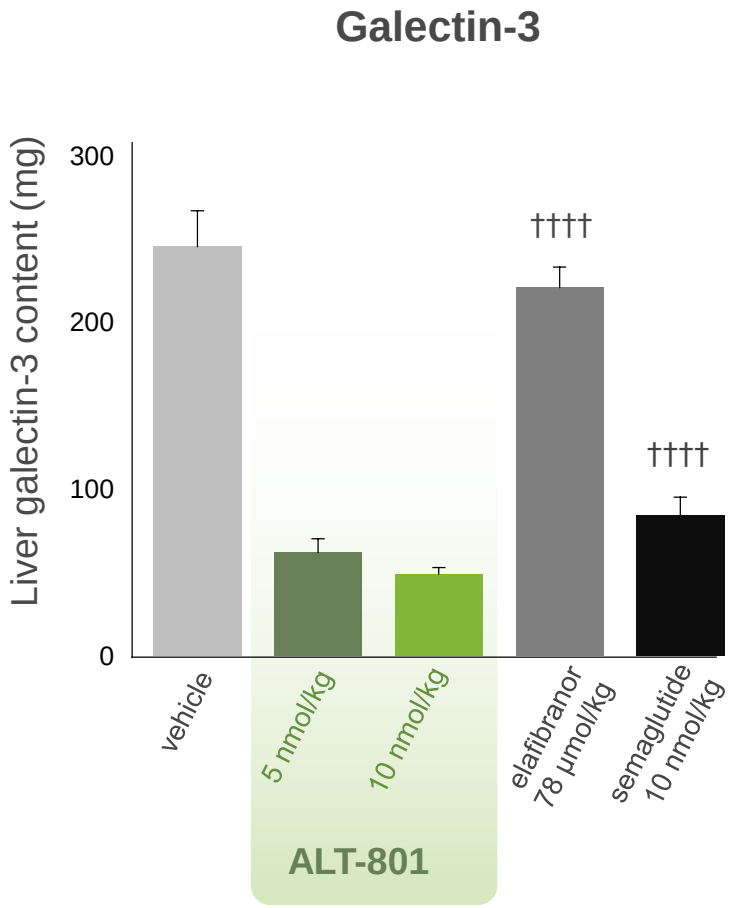
ALT-801
GREATER EFFECTS ON FIBROSIS

Gubra NASH Mouse Model After 12 Weeks of Treatment





Mean (SE), 1-way ANOVA with Dunnett's adjustment for multiplicity
†† p < .01, ††† p < .001, ††††, p < .0001 vs. **ALT-801** 10 nmol/kg (n=11-12)

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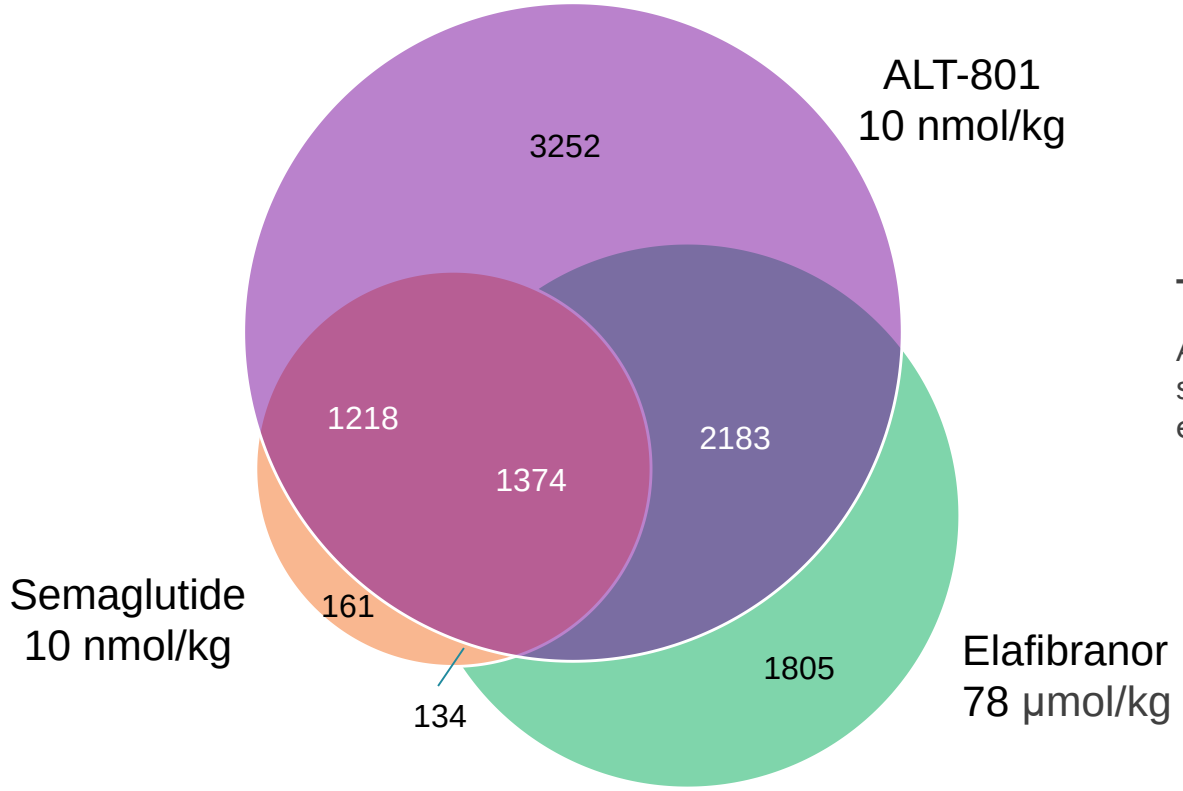
PLEIOTROPIC EFFECTS

ALT-801 DIFFERENTIALLY REGULATED MORE PATHWAYS IN NASH PATHOGENESIS



Total regulated genes

ALT-801 10nmol/kg ~ 8,000
semaglutide 10nmol/kg ~ 2,800
elafibranor 78µmol/kg ~ 5,800

Visualization of the number of genes regulated by each compound. Values inside circles indicate the number of genes differentially expressed versus the vehicle group that are compound specific or shared between treatments.

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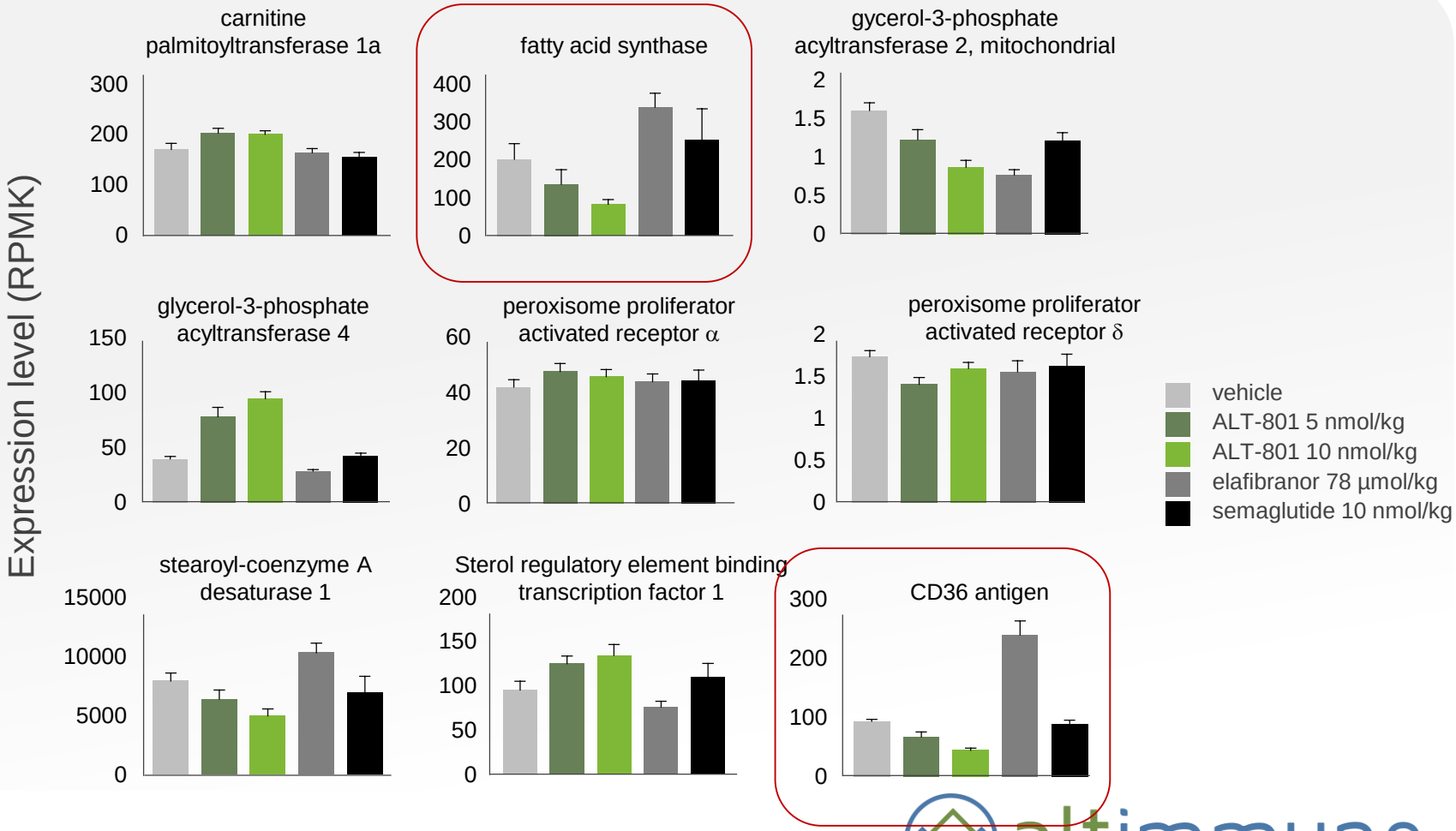
ALT-801

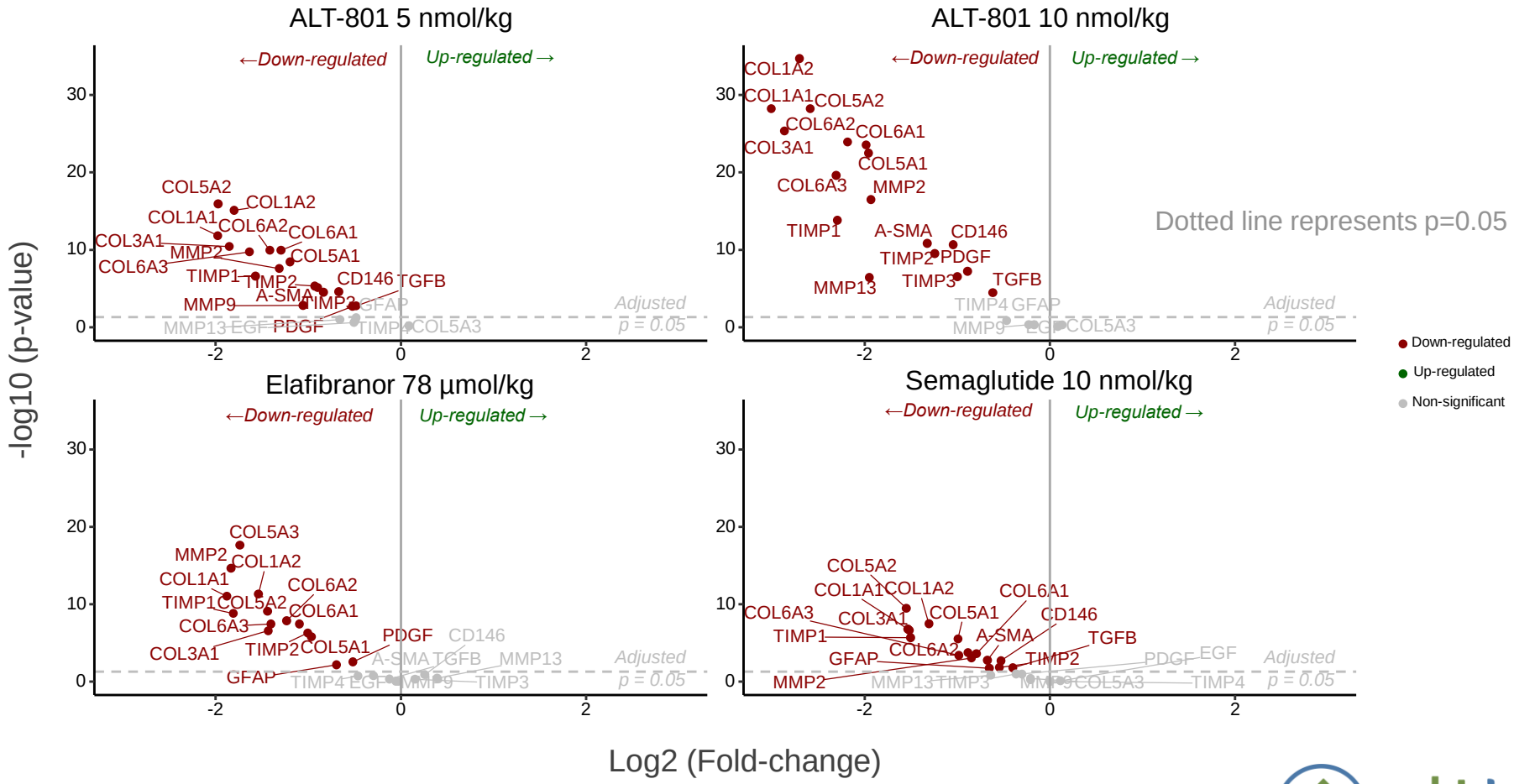
MODULATES GENES AFFECTING FAT METABOLISM AND TRANSPORT

Gubra NASH Mouse Model After 12 Weeks of Treatment



ALT-801

GREATER SUPPRESSION OF PRO-FIBROTIC STELLATE CELL GENES



ALT-801
SUMMARY

- NASH is a disease of obesity
- Drugs for treatment of NASH and NASH-related complications should target 10% or greater body weight loss
- ALT-801 resulted in superior reductions in nearly all measured NASH parameters compared to semaglutide or elafibranor in a preclinical model, returning many parameters to lean normal range
- In this model, ALT-801 also exhibited pleiotropic effects across multiple pathways involved in NASH pathogenesis

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ALT-801
CONCLUSIONS

- The improvements of body weight, liver pathology and metabolic parameters in this NASH model highlight ALT-801 as an attractive new drug candidate for the treatment of NASH

- First-in-man studies are expected to commence Q4 2020

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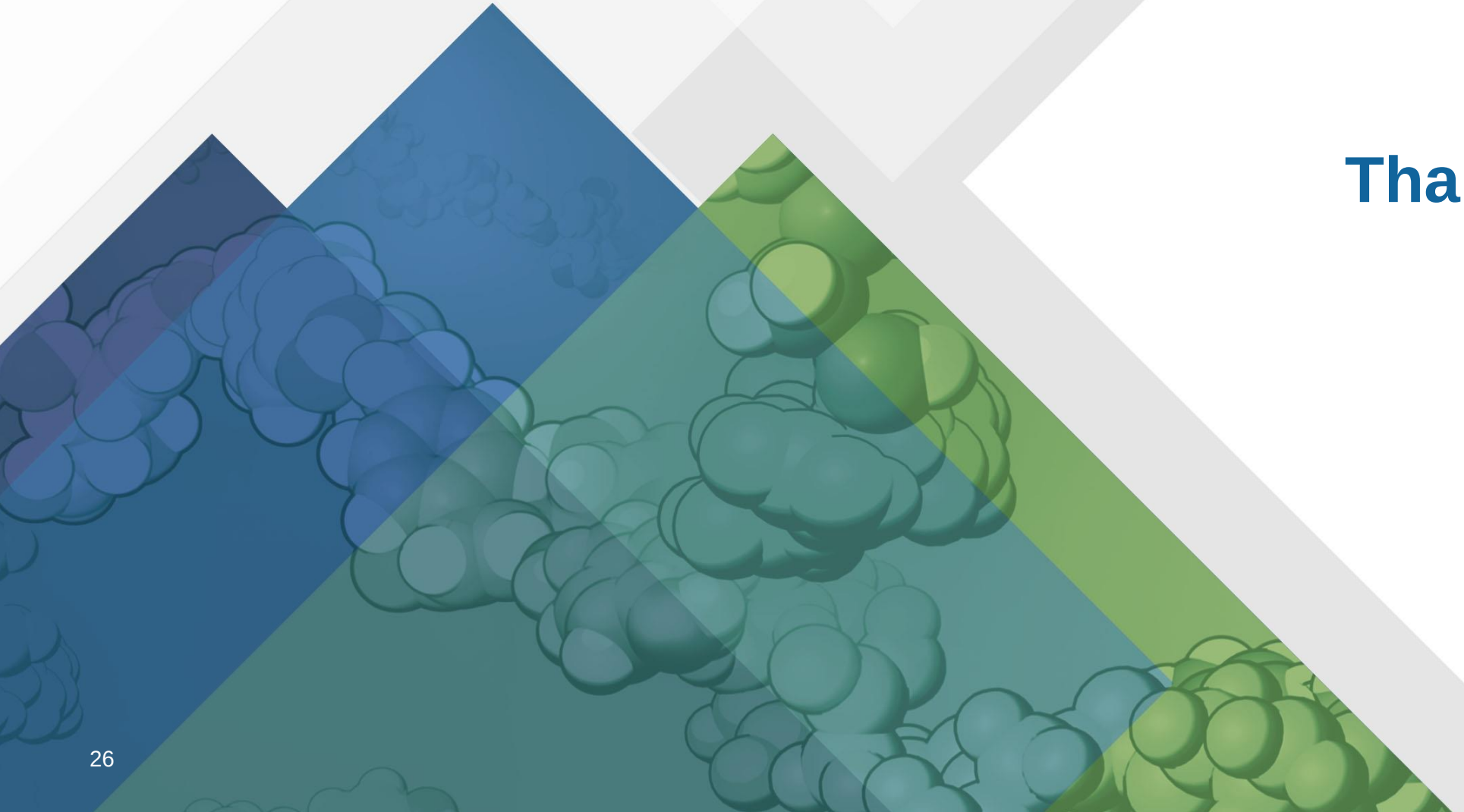
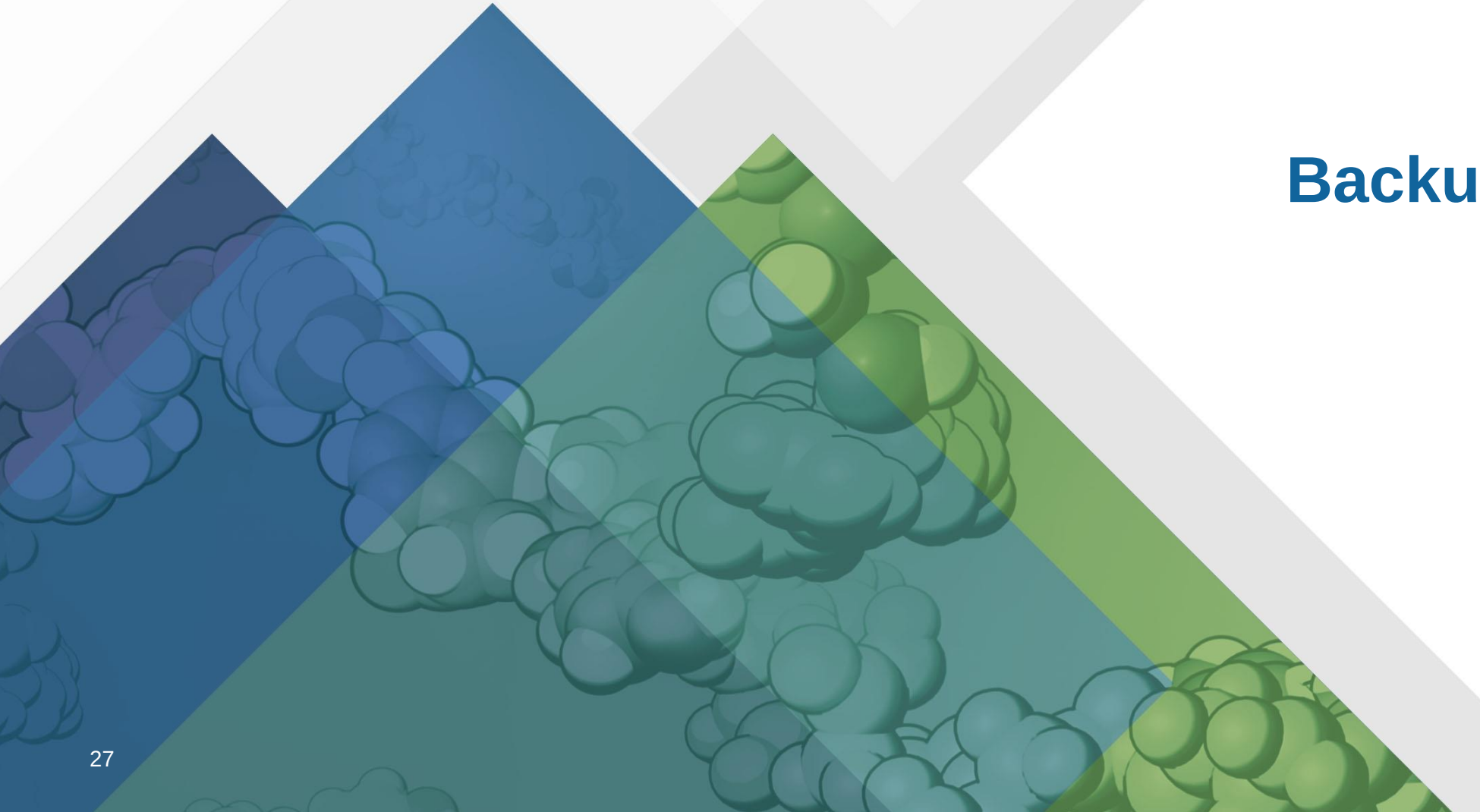


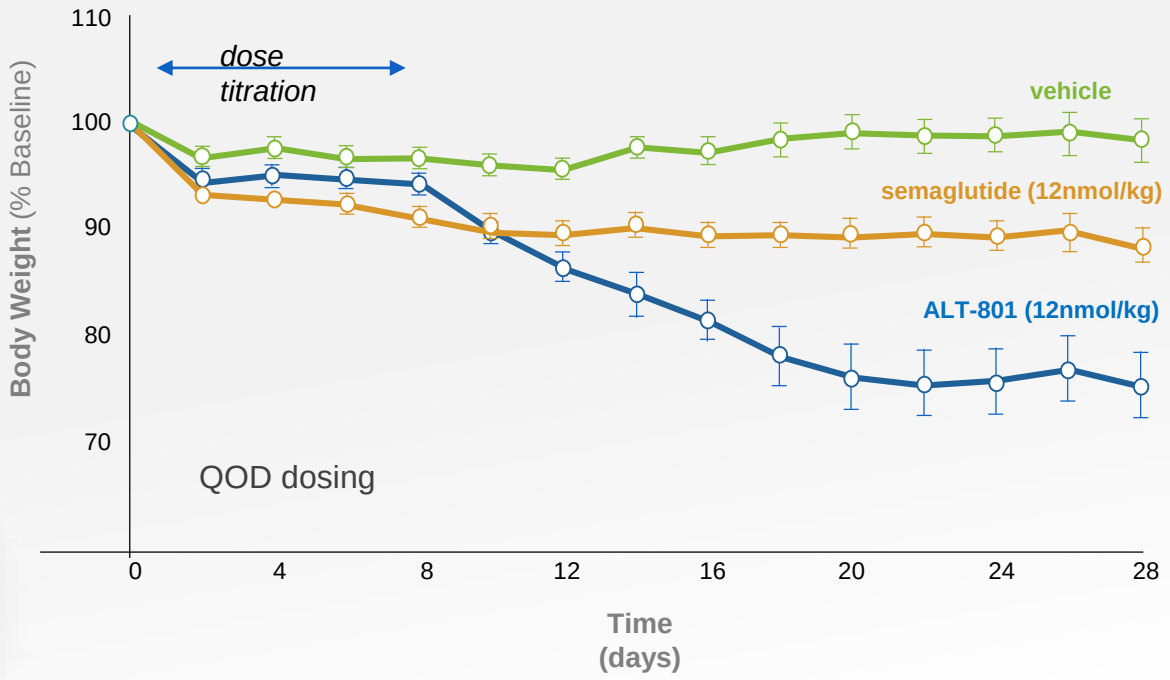
Thank You

Backup Slides



ALT-801
DOUBLE THE WEIGHT LOSS COMPARED TO SEMAGLUTIDE

JAX DIO Model After 4 Weeks of Treatment



- Mice receiving ALT-801 achieved 2.5x the weight loss of semaglutide-treated animals (25% vs. 10%) despite similar decreases in food intake
- Body weights of ALT-801 mice returned to lean normal levels
- Mice pair-fed to mimic the effects of on food consumption achieved only 5% weight loss

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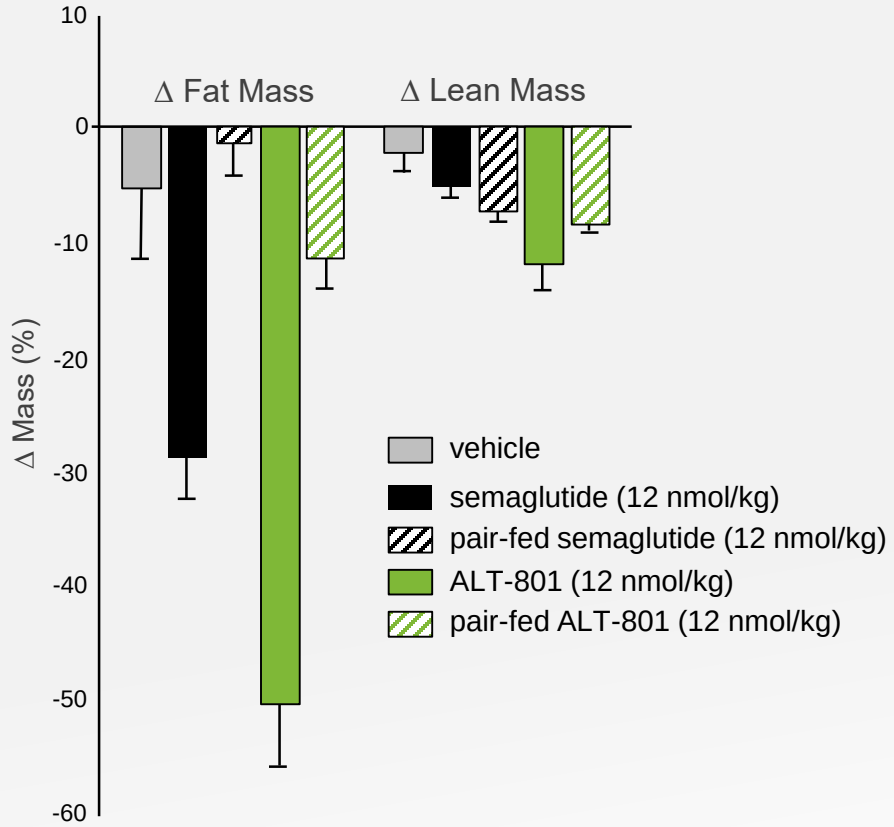
ALT-801
REDUCTIONS IN FAT MASS—JAX DIO MICE (DAY 28)



- ALT-801-treated animals achieved ~2x the fat loss of semaglutide-treated animals (51% vs. 28%) and >4x pair-fed animals
- Relative preservation of lean mass

Industry Landscape

DUAL GLP-1/GLUCAGON AGONISTS IN DEVELOPMENT

Company	Molecule	Status/ Phase	Frequency of Administration	Side Chain	Ratio in vitro
Altimmune	ALT-801	Preclinical	Weekly	EuPort™	Balanced
Hanmi	HM12525A	2	Weekly	IgG	Balanced
Transition / Lilly /OPKO	LY2944876 / TT401	Terminated	Weekly	PEG	>10:1 bias toward GLP-1R
OPKO (Prolor)	Pegapamodutide OPK88003/MOD6030	2	Weekly	PEG	Balanced
Novo Nordisk	NNC9204-1177	1	Weekly	Free carboxylate on fatty acid	Believed to be 3:1 biased to GLP-1R
BI/Zealand	BI 456906 US 2018/0094038 A1	2	Weekly	Free carboxylate on fatty acid	7.5:1 bias toward GLP-1R
Astra Zeneca	Cotadutide MEDI0382	2	Daily	Palmitoyl	5:1 biased toward GLP-1R
Sanofi-Aventis	SAR425899	Terminated	Daily	Palmitoyl	5:1 biased toward GLP-1R