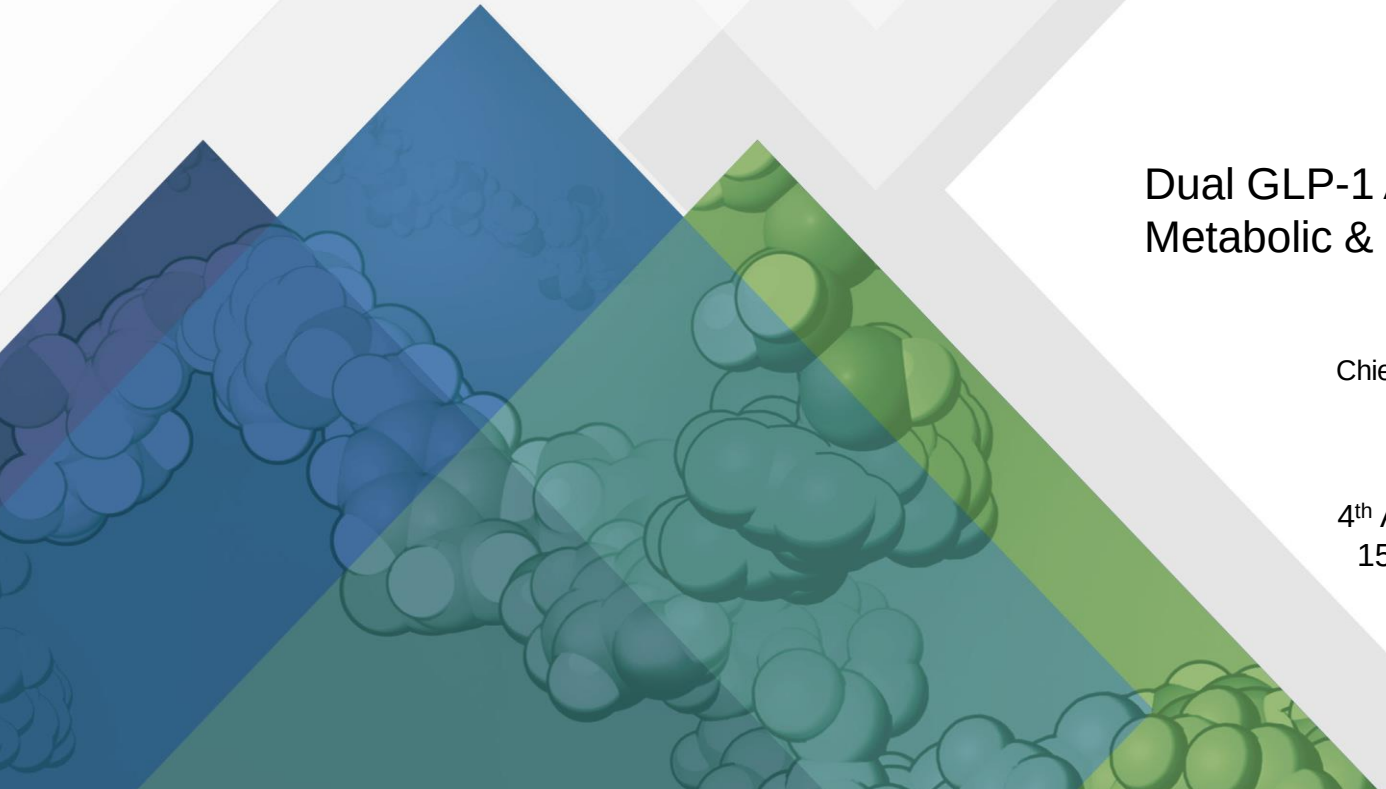


Dual GLP-1 Agonists in the Treatment Metabolic & Liver Dysfunction in NASH

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

4th Annual NASH Summit
15-18 December 2020

altimmune

NASH AND NAFLD

HEPATIC MANIFESTATIONS OF OBESITY AND METABOLIC SYNDROME

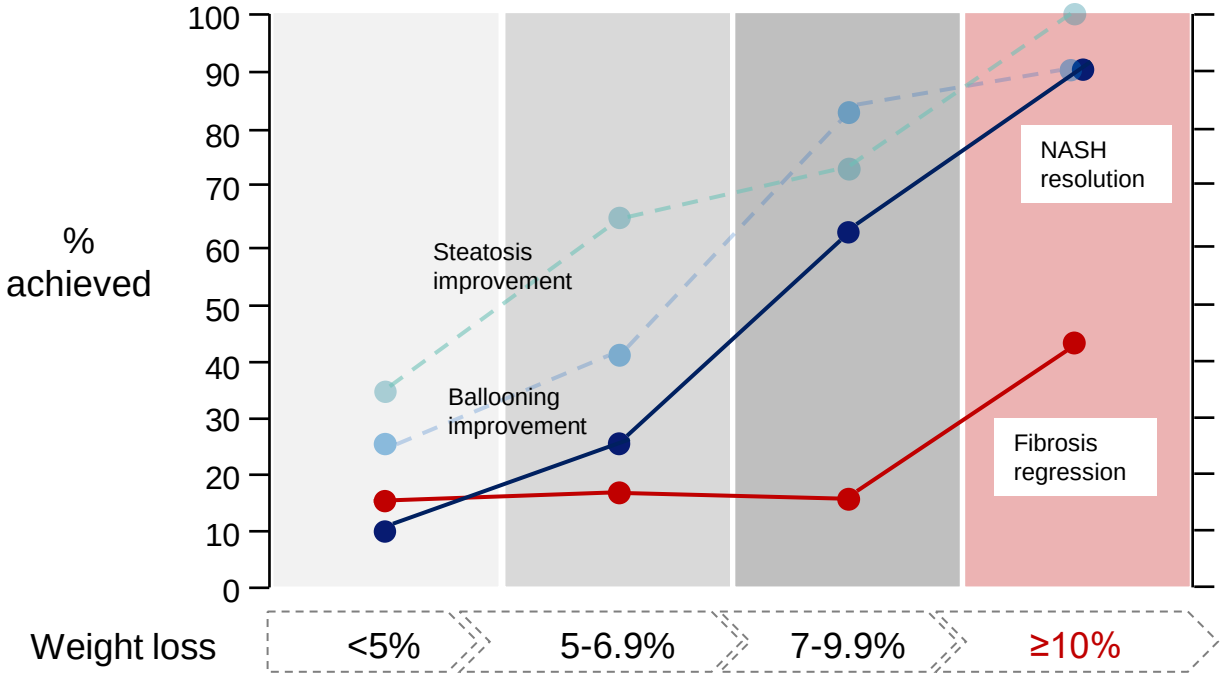
- NAFLD is present in up to **90% of obese patients**, and **~20%** of NAFLD patients **progress to NASH**[1]
- Up to **40% of NASH patients develop NAFLD** recurrence one year after liver transplant—we believe the underlying metabolic disease is still present[2]
- The **treatment of obesity** is the cornerstone of treating NASH and the principal morbidities of NASH[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

altimmune

SUBSTANTIAL BODY WEIGHT LOSS IS NECESSARY TO BLUNT NASH PROGRESSION

10% OR MORE WEIGHT LOSS MUST BE ACHIEVED[1]



The **treatment of obesity** remains the cornerstone of NASH and NAFLD therapy

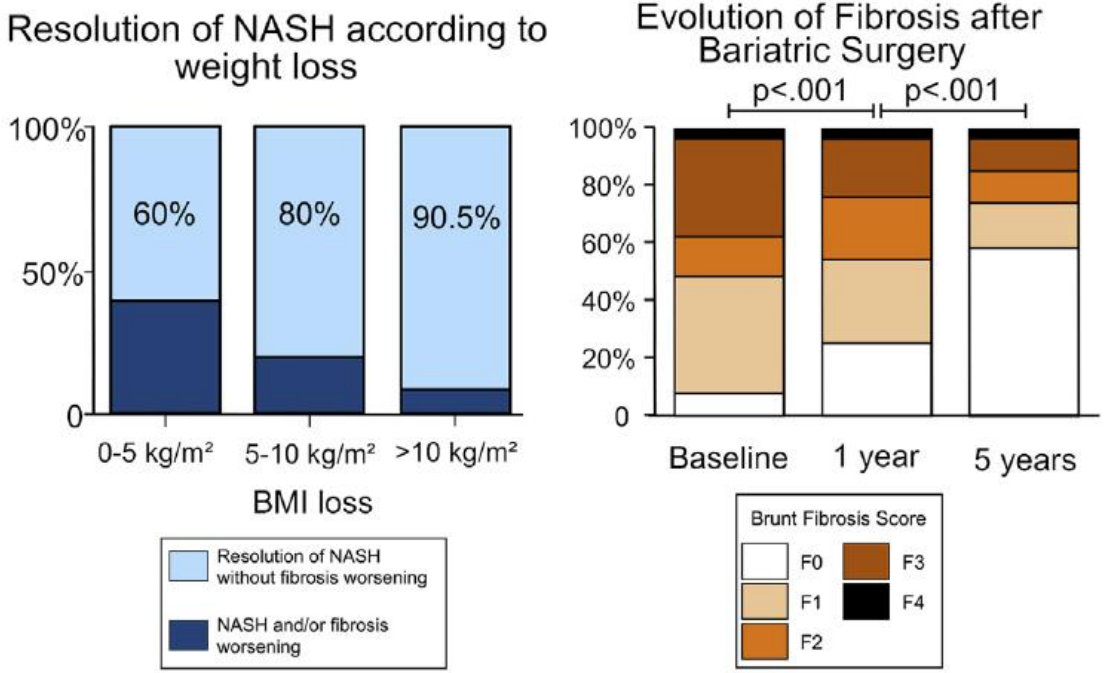
Meaningful weight loss is rarely achieved without medical intervention

Current drugs have failed to deliver the weight loss achieved by bariatric surgery

[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 and adapted from Harrison, EASL 2019, Traber, Discovery on Target: Targeting NASH 2019*

altimmune

BARIATRIC SURGERY PROVIDES LONG-TERM RESOLUTION OF NASH AND REGRESSION OF FIBROSIS



Lassaily, Gastroenterology 2020;159:1290–1301

NAFLD—CAUSES OF DEATH

MOST DEATHS REFLECT COMPLICATIONS OF OBESITY RATHER THAN LIVER DISEASE

Outcome	n (%)
Death or liver transplantation	193 (31.2)
Cardiovascular disease	74 (12.0)
Non-liver cancer	36 (5.8)
Cirrhosis complications	15 (2.4)
Infections	15 (2.4)
Liver transplantation	1 (0.2)
Other	35 (5.7)
Cirrhosis events	26 (4.2)
Variceal bleeding	12 (1.9)
Ascites	9 (1.5)
Encephalopathy	6 (1.0)
Hepatorenal syndrome	4 (0.6)
Spontaneous bacterial peritonitis	3 (0.5)
Hepatocellular cancer	3 (0.5)
Hepatopulmonary syndrome	2 (0.3)

619 patients with biopsy confirmed NAFLD (1975-2005)

Median follow-up 12.6 years (range 0.3-35)

Adapted from Angulo, Gastroenterology 2015;149: 389–397

altimmune

SNAPSHOT OF COMPOUNDS IN ADVANCED NASH DEVELOPMENT

MOST AGENTS FAIL TO ACHIEVE MEANINGFUL LEVELS OF WEIGHT LOSS

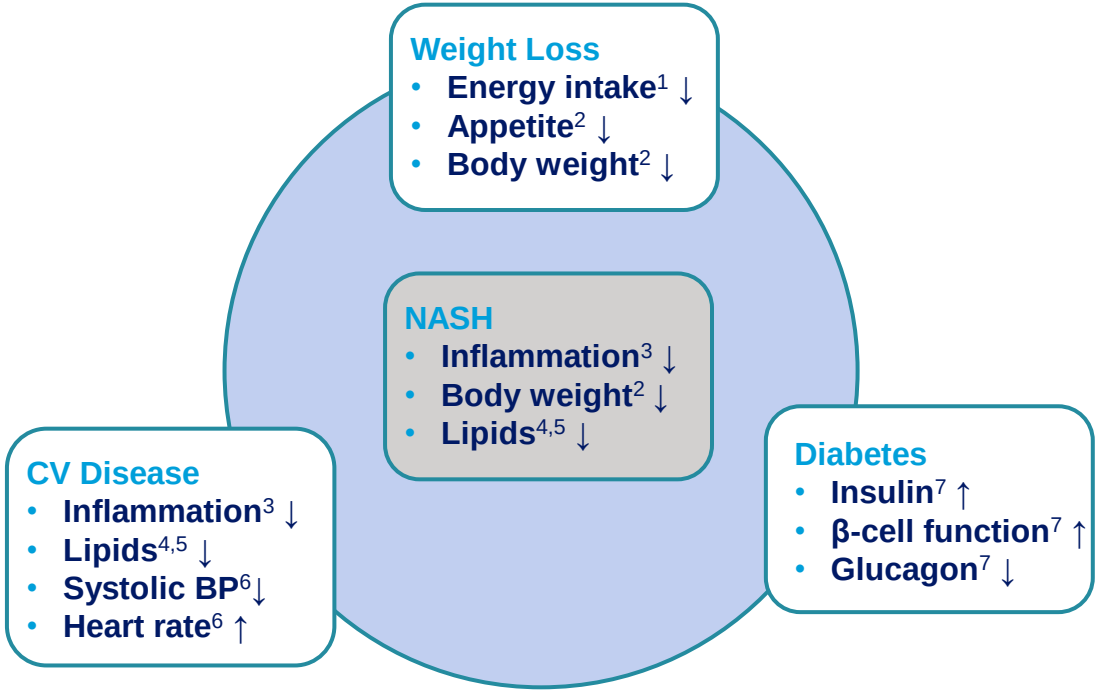
Agent	Author (year)	Mechanism	Weight Loss (%)
Obeticholic acid	Younossi, ZM 2019[1]	FXR agonist	~2%
Resmetirom	Harrison, SA 2018[2]	THRβ agonist	no change
Aldafermin (3mg)†	Harrison, SA 2019[3]	FGF19 agonist	1.3%
Pegbelfermin (10 mg)††	Sanyal, A 2018[4]	FGF21 agonist	2.2%
AKR-001 (70 mg)	Ritchie, M 2020[5]	FGF21 agonist	no change[5]; 3.7%†††
Firsocostat	Lawitz, EJ 2018[6]	ACC inhibitor	no change
Lanifibranor (1200 mg)	Franque, S 2020[7]	PanPPAR	increases 3.1%

† No information has been made public on 1mg dose
†† Gain of 0.6% on 20mg dose
††† BALANCED study (June 30 corporate deck)

[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]Ritchie, M, et al. (2020) Exp Opin Invest Drugs, 29:2, 197-204; [6] Lawitz, EJ, et al. (2018) Clin Gastroenterol Hepatol 16:1983-91; [7]Franque S, AASLD 2020

altimmune

GLP-1 ANALOGUES HAVE MULTIPLE BENEFICIAL EFFECTS

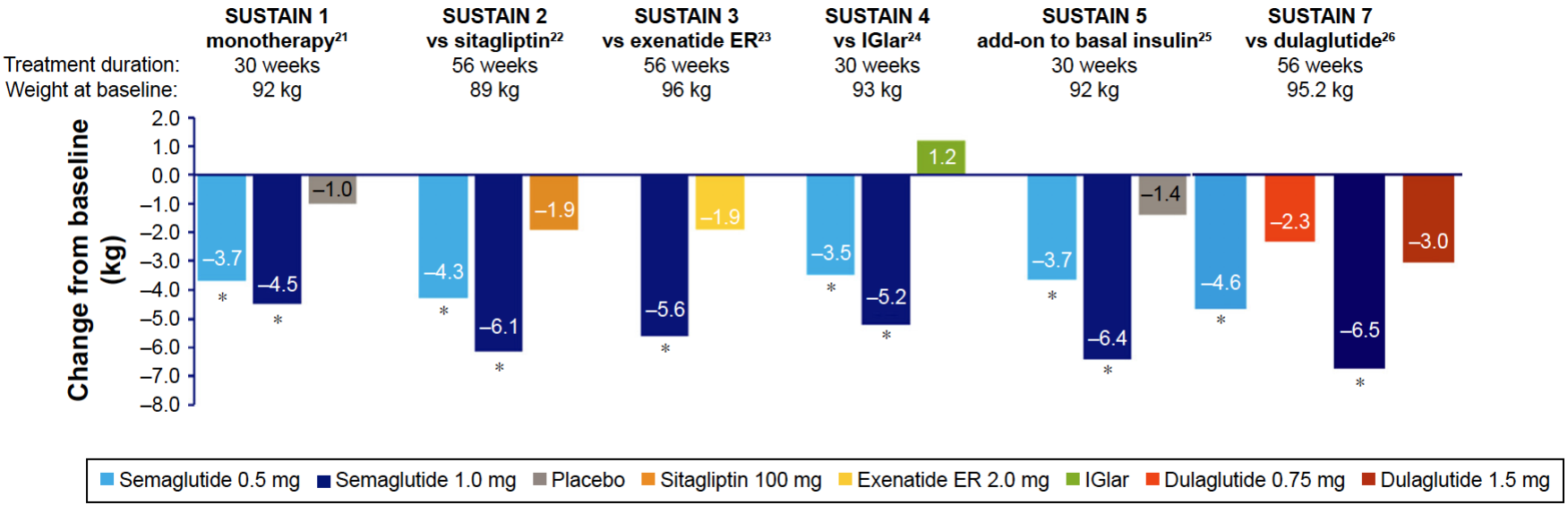


1 Bagger JI, *et al. J Clin Endocrinol Metab* 2015;100:4541–52; 2 Flint A, *et al. J Clin Invest* 1998;101:515–20.; 2 Tong J and D'Alessio D. *Diabetes* 2014;63:407–9; 3 Hogan AE, *et al. Diabetologia* 2014;57:781–4; 4 Hermansen K, *et al. Diabetes Obes Metab* 2013;15:1040–8; 5 Ahrén B, *et al. Lancet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

altimmune

SEMAGLUTIDE SUSTAIN TRIALS (0.5 – 1.0 MG/WEEK)

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



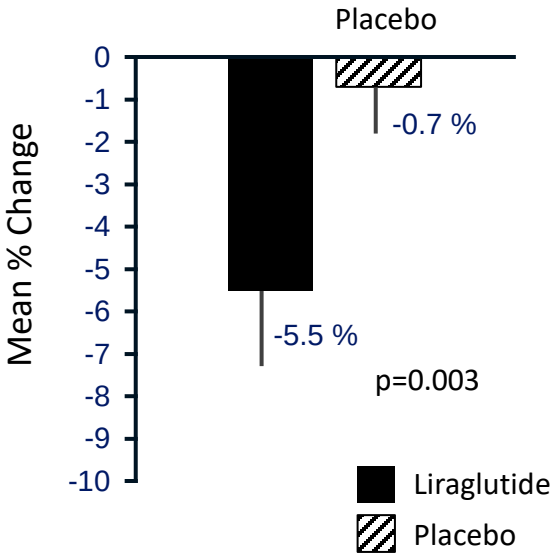
Gomez-Peratta F, et al, Drug Design, Development and Therapy 2019:13 731–738

8

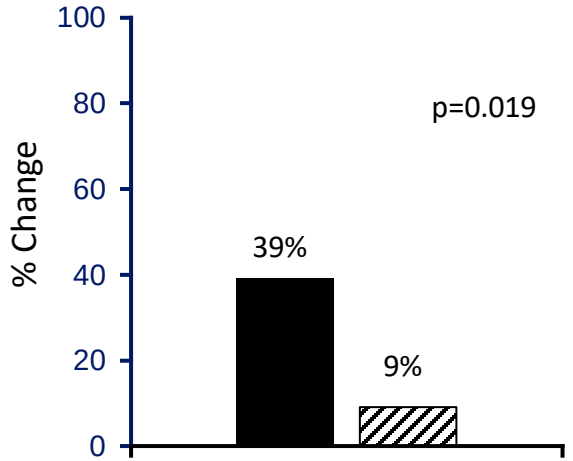
LEAN TRIAL—WEIGHT LOSS AND NASH RESOLUTION

LIRAGLUTIDE 1.8 MG DAILY FOR 48 WEEKS

Weight Loss



NASH Resolution



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

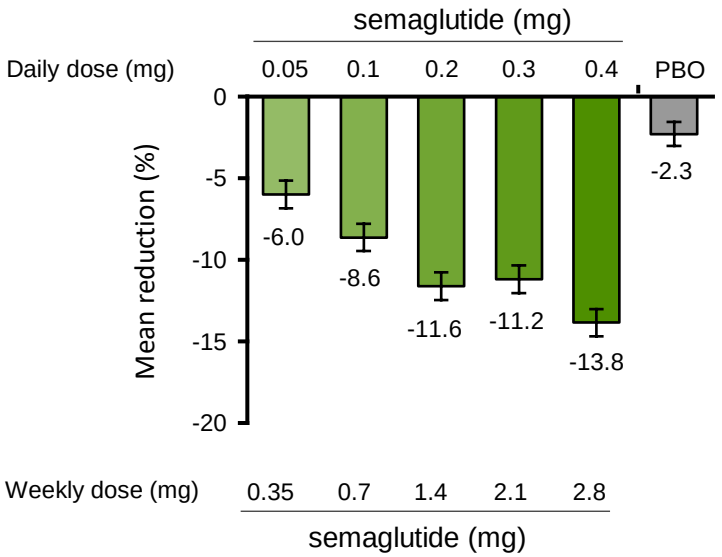
altimmune

9

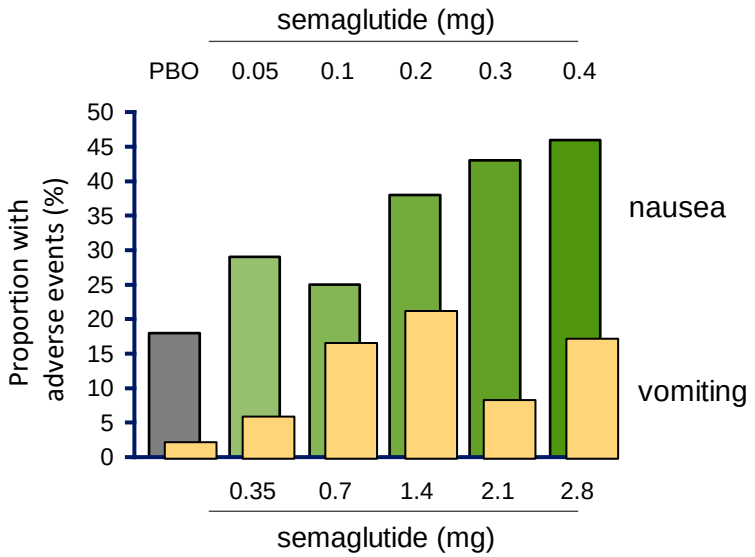
SEMAGLUTIDE OBESITY TRIAL

WEIGHT LOSS DRIVEN AT THE EXPENSE OF GI SIDE EFFECTS AND EXTENDED DOSE-TITRATION

Body Weight



Nausea and Vomiting



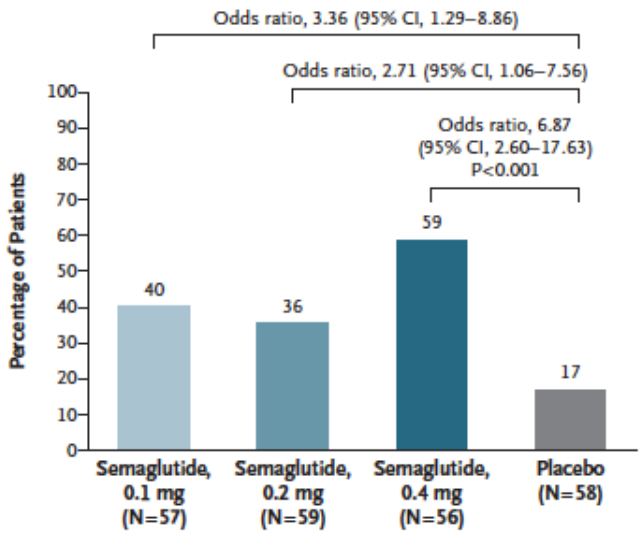
Adapted from O'Neil PM, et al. Lancet 2018;392:637–49

10

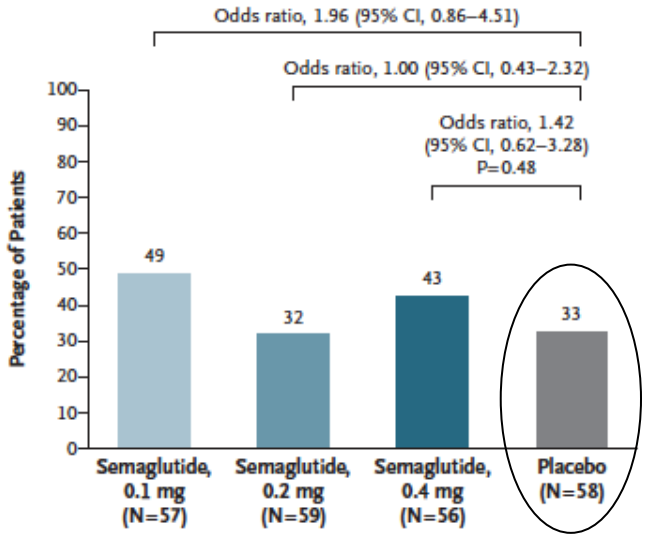
SEMAGLUTIDE NASH TRIAL

FIBROSIS IMPROVEMENT CONFOUNDED BY UNUSUALLY HIGH PLACEBO RESPONSE

NASH Resolution



Fibrosis Improvement



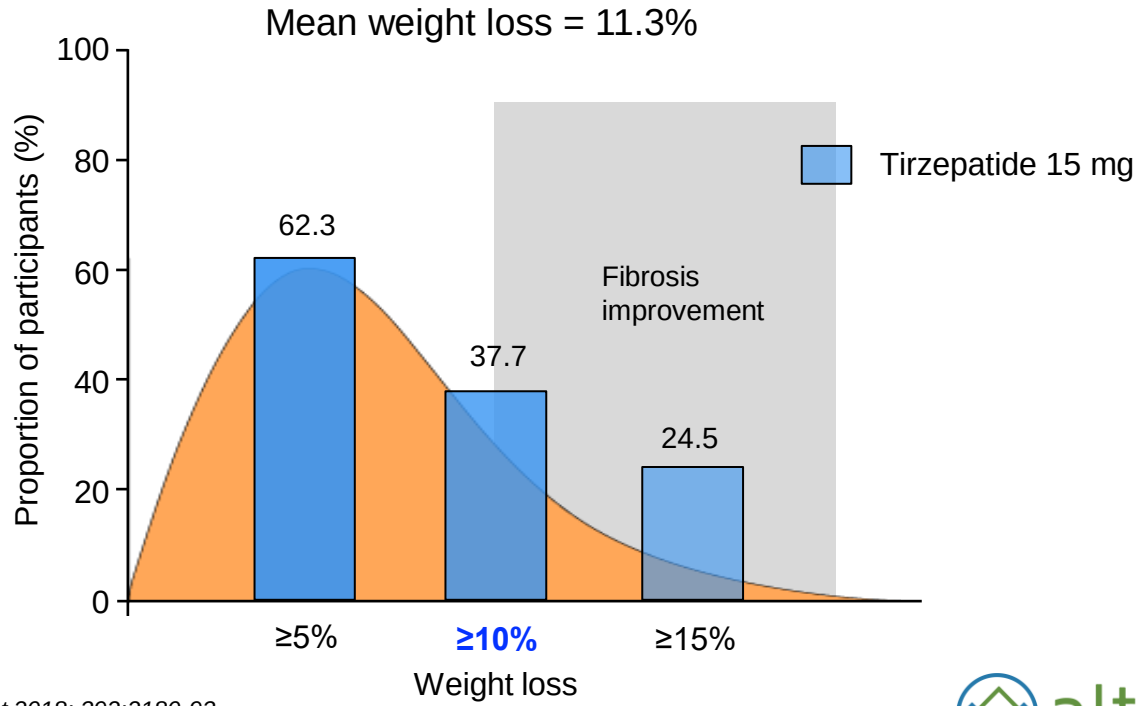
Newsome, NEJM 2020; Nov 13. doi: 10.1056/NEJMoa2028395

altimmune

11

MEAN WEIGHT LOSS COULD OVERREPRESENT NASH BENEFIT

11.3% MEAN LOSS = ONLY 37.7% ACHIEVE THE VILAR-GOMEZ FIBROSIS IMPROVEMENT THRESHOLD



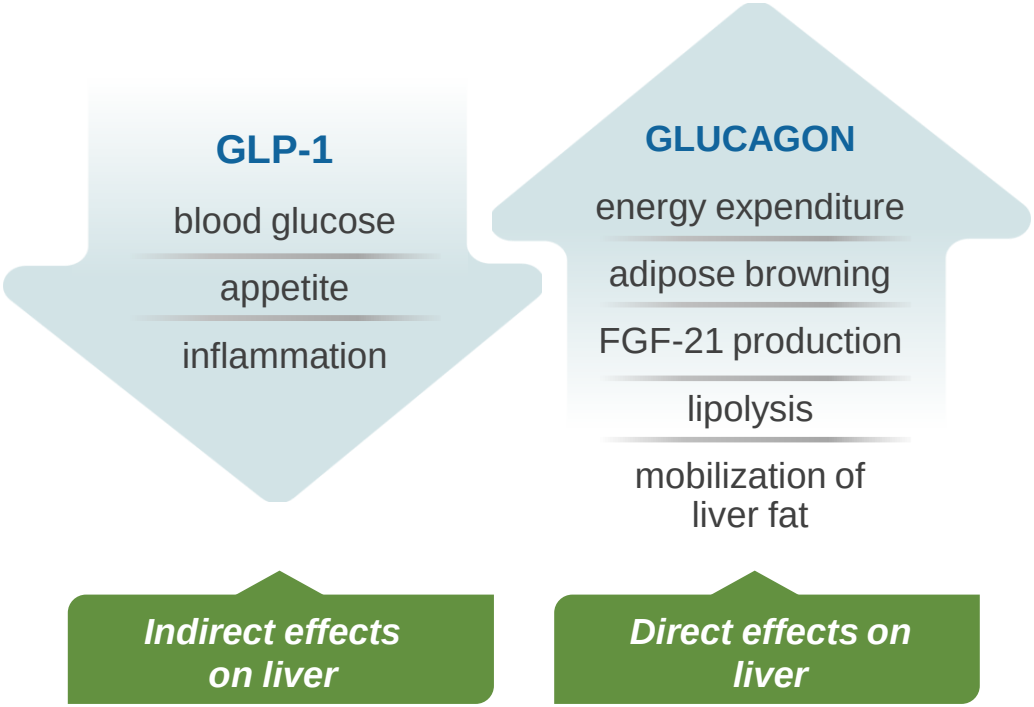
Adapted from Frias JP, Lancet 2018; 392:2180-93

altimmune

12

GLP-1/GLUCAGON RECEPTOR DUAL AGONISTS

OPTIMIZED FOR NASH AND WEIGHT LOSS

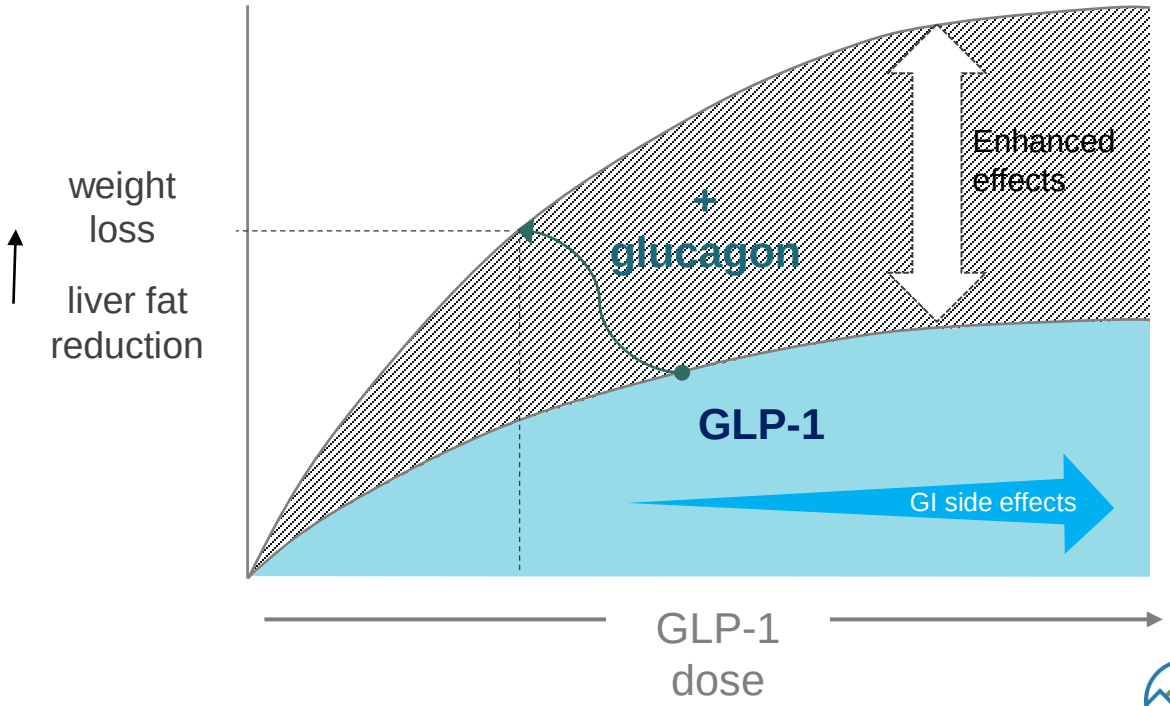


Sanchez-Garrido MA, Diabetologia (2017) 60:1851–1861; Soni H, Med Hypotheses 95 (2016) 5–9; Salem V, Diab Obes Metab 18: 72–81, 2016; Scot R, Peptides 104 (2018) 70–77

altimmune

GLUCAGON WITH GLP-1 AGONISM

POTENTIATES SYNERGISTIC EFFECTS ON WEIGHT AND LIVER FAT REDUCTION



altimmune

INDUSTRY LANDSCAPE

GLP-1/GLUCAGON DUAL AGONISTS IN DEVELOPMENT

Company	Molecule	Status/ Phase	Frequency of Administration	Side Chain	GLP-1R/GCGR Ratio in vitro
Altimmune	ALT-801	1	Weekly	EuPort™	Balanced
Merck/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	Terminated	Weekly	Free carboxylate on fatty acid	3:1 bias towards 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 bias toward GLP-1R
Sanofi-Aventis	SAR425899	Terminated	Daily	Palmitoyl	5:1 bias toward GLP-1R

BALANCED 1:1 GLP-1/ GLUCAGON AGONISM

KEY TO ACHIEVING IMPROVED EFFECTS ON NASH AND WEIGHT LOSS

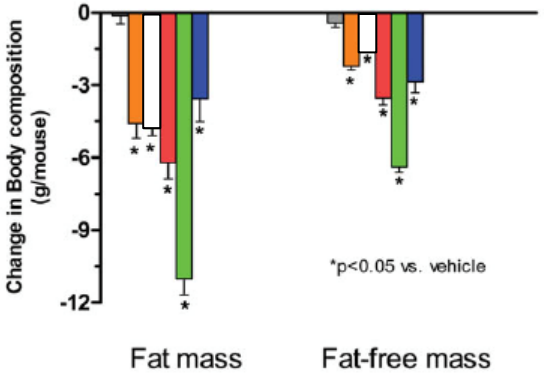
- Sustained effects on both receptors are necessary to achieve improved weight loss
- Single receptor-biased ligands retain effects on only one receptor over a prolonged dosing period[1]
- By achieving 1:1 balance, the synergies of GLP-1 and glucagon are maintained throughout the entire dosing period

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

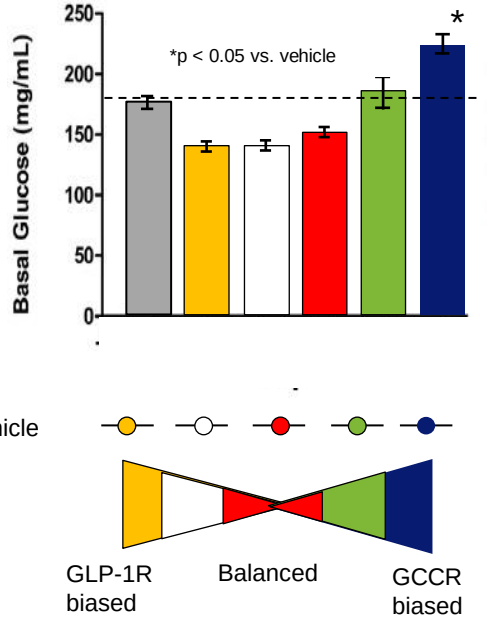
altimmune

BALANCED (1:1) AGONISTS EXERT OPTIMAL EFFECTS

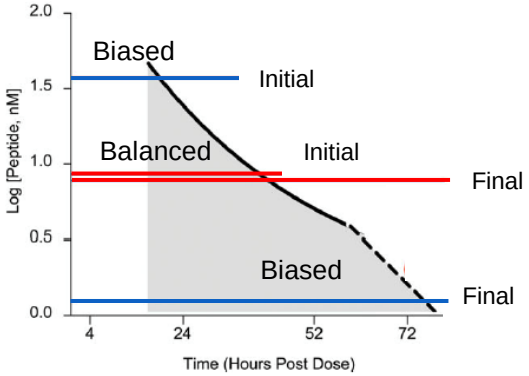
Fat / Fat-Free Mass



Serum Glucose



Peptide concentration

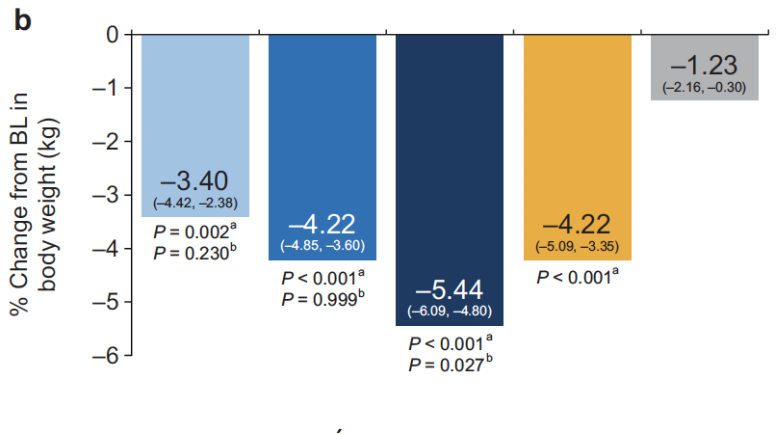


Adapted from Day JA, Peptide Science 2012;98:443-50

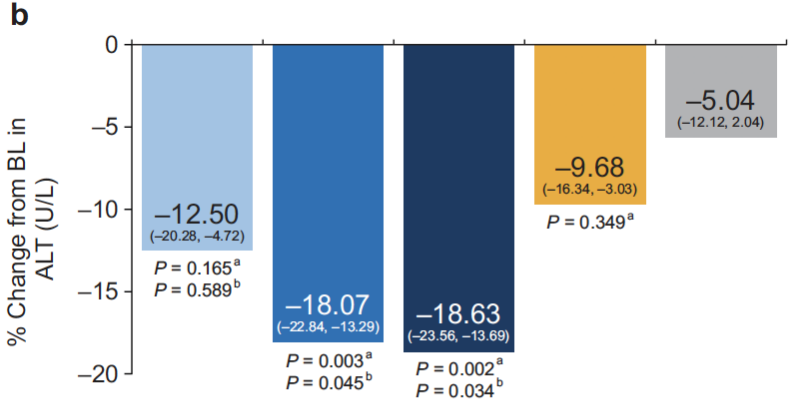
COTADUTIDE—5:1 GLP-1R/ GCGR RATIO

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; Ambery EASL (DILC) 2020

COTADUTIDE—ADVERSE EVENTS

HIGH INCIDENCE OF GI INTOLERANCE WHEN GLP-1 PREDOMINATES

Summary of Treatment-Emergent Adverse Events (TEAEs), n (%)

	Cotadutide 100 µg (n = 100)	**Cotadutide 200 µg** (n = 256)	**Cotadutide 300 µg** (n = 256)	Liraglutide 1.8 mg (n = 110)	Placebo (n = 112)
TEAEs (total)	64 (64)	190 (74)	188 (73)	57 (52)	60 (54)
TEAEs leading to discontinuation	11(11)	37 (15)	51 (20)	2 (2)	4 (4)
Gastrointestinal TEAEs	37 (37)	145 (57)	146 (57)	26 (24)	26 (23)
Nausea	23 (23)	85 (33)	104 (41)	16 (15)	12 (11)
Vomiting	10 (10)	50 (20)	41 (16)	2 (2)	3 (3)
Diarrhea	11 (11)	46 (19)	26 (10)	4 (4)	10 (9)

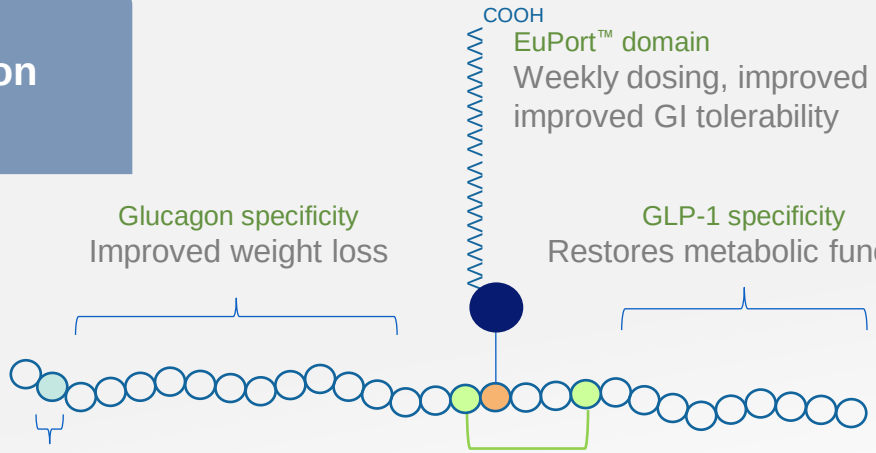
Nahra R et al, AASLD 2019

altimmune

ALT-801

BALANCED (1:1) DUAL AGONIST WITH ENHANCED PHARMACOKINETIC PROPERTIES

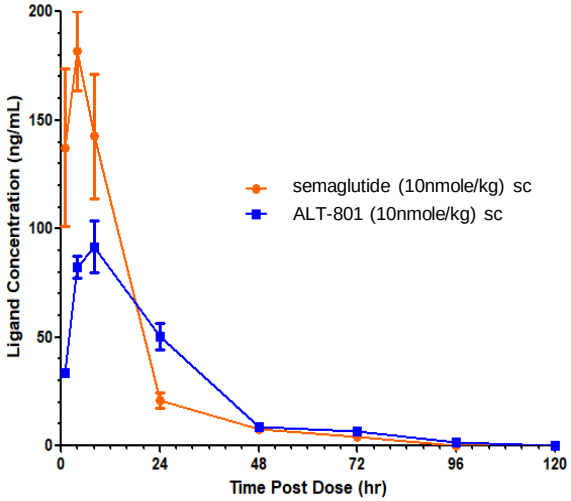
Balanced (1:1) GLP-1:Glucagon Agonism



[1]Guarracino DA et al., Chem Rev. 2019 Sep 11;119(17):9915-9949

altimmune

EUPORT™ DOMAIN PROVIDES REDUCED CMAX AND IMPROVED TOLERABILITY AFTER SC ADMINISTRATION

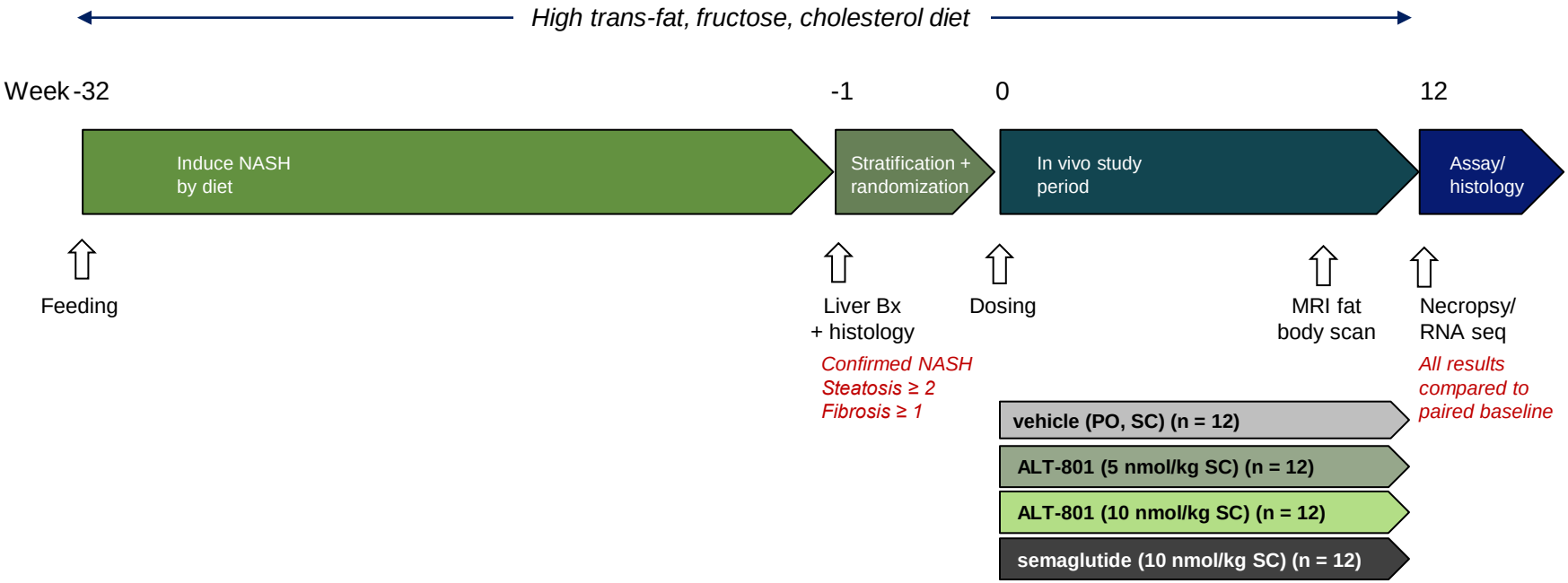


- The micellar properties of EuPort™ slow entry of ALT-801 into the bloodstream after injection, lowering C_{max} (peak concentration)
- Lower C_{max} is associated with improved GIP-1RAs tolerability[1]

[1]*Bettge, K., et al. (2017) Diabetes Obes Metab (2017) 19: 336-347*

ALT-801

GUBRA AMYLIN NASH MODEL IN MALE C57BL/6J MICE



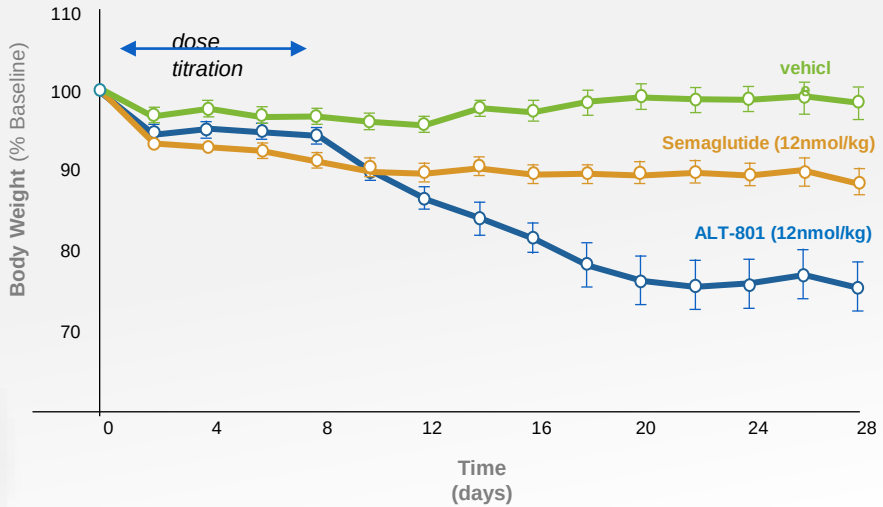
Hansen, HH, et al. (2017) Drug Disc Today 22 (11): 1707-18

altimmune

ALT-801

25% REDUCTION IN BODY WEIGHT TO CHOW-FED LEAN NORMAL RANGE

Mouse DIO Model After 4 Weeks of Treatment



More than **2x** the weight loss of **semaglutide**

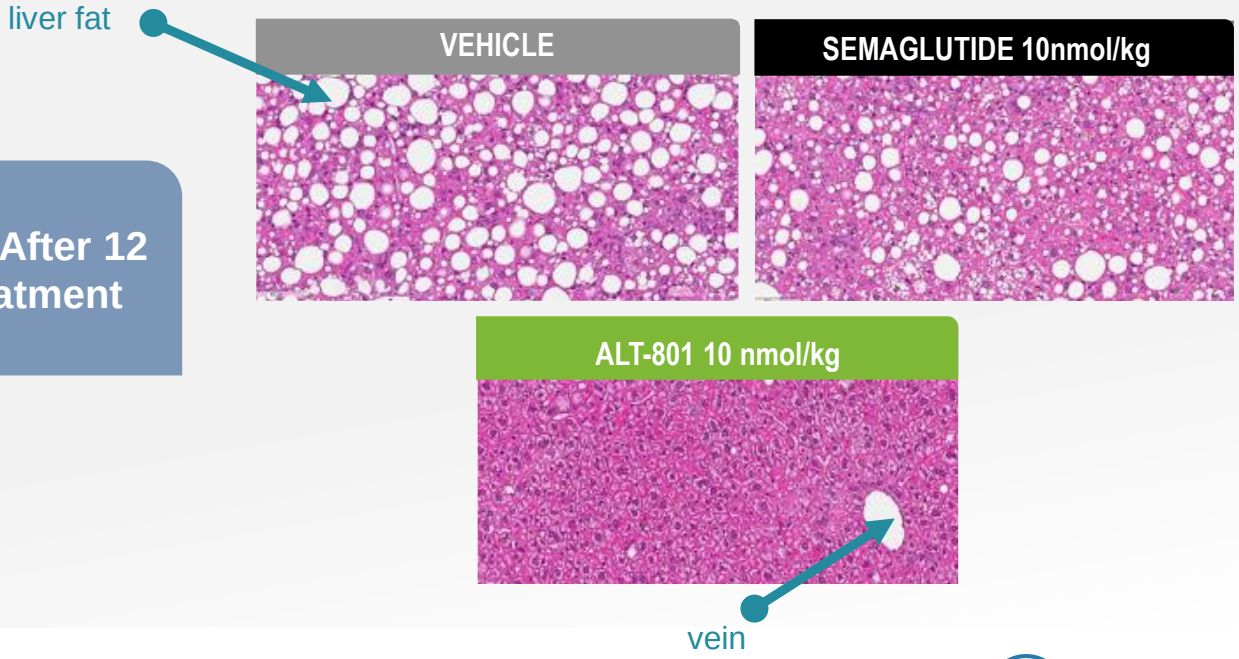
Body weight decreased to **lean normal range**

altimmune

ALT-801

REDUCTION IN LIVER FAT AND LIVER WEIGHT TO LEAN NORMAL RANGE

Gubra Model After 12 Weeks of Treatment

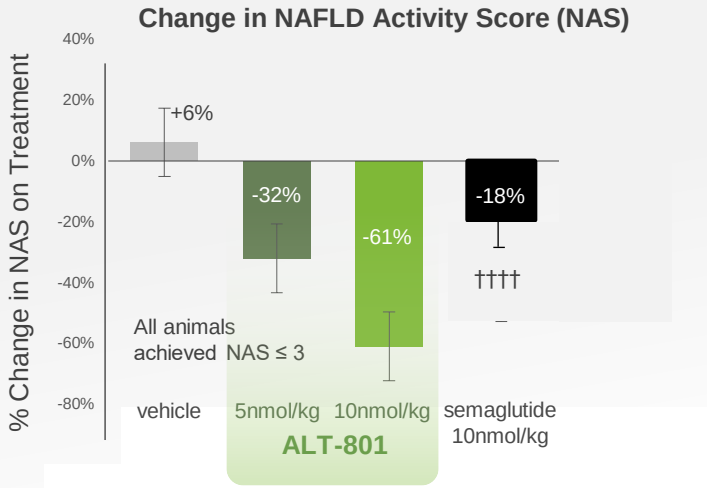


altimmune

ALT-801

GREATER REDUCTION IN NAFLD ACTIVITY SCORE (NAS)

Gubra NASH Mouse Model After 12 Weeks of Treatment



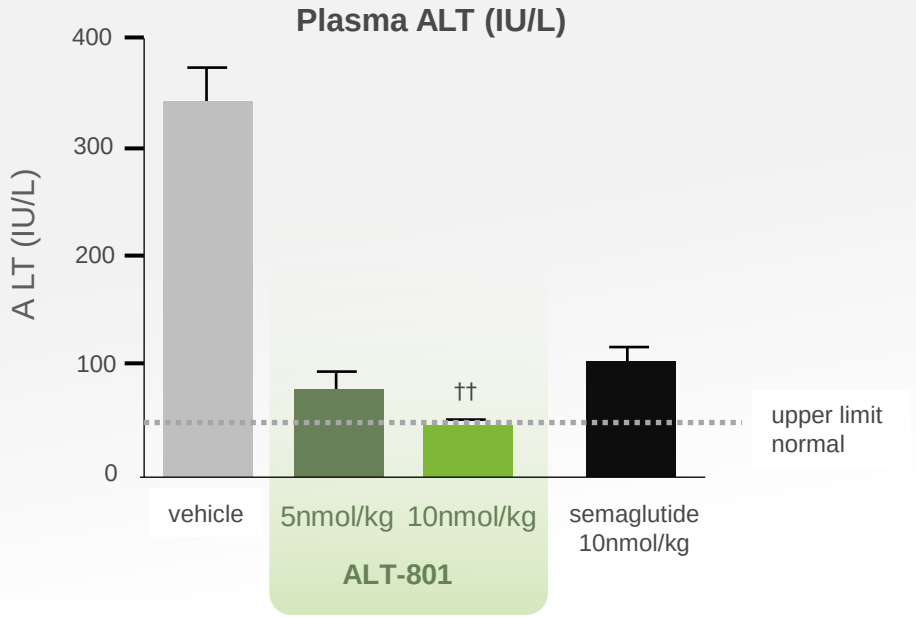
Mean (SE), 1-way ANOVA with Dunnett's adjustment for multiplicity
†† p < .01, ††† p < .001, ††††, p < .0001 vs. ALT-801 10 nmol/kg (n=11-12)

altimmune

ALT-801

NORMALIZATION OF PLASMA ALANINE AMINOTRANSFERASE (ALT)

Gubra NASH Mouse Model After 12 Weeks of Treatment



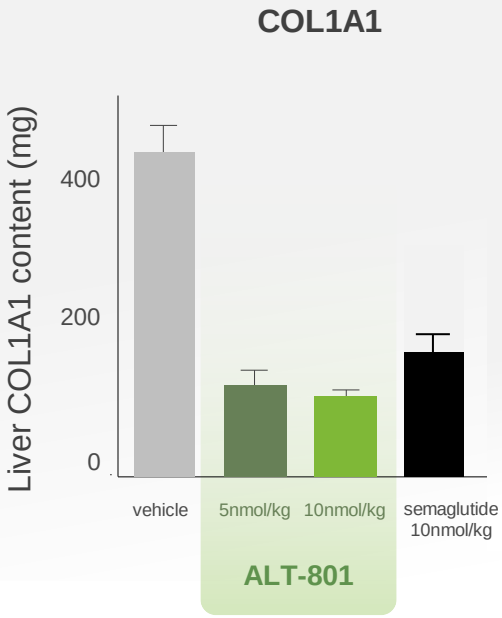
Mean (SE), 1-way ANOVA with Dunnett's adjustment for multiplicity
†† p < .01, ††† p < .001, †††† p < .0001 vs. semaglutide (n=11-12)

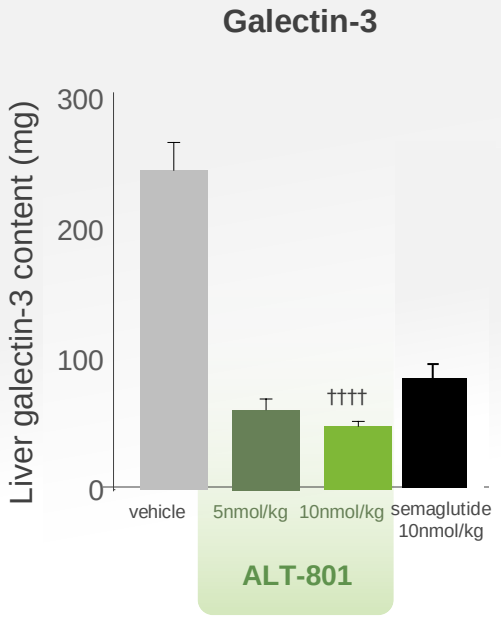
altimmune

ALT-801

GREATER EFFECTS ON FIBROSIS AND INFLAMMATION

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. semaglutide (n=11-12)

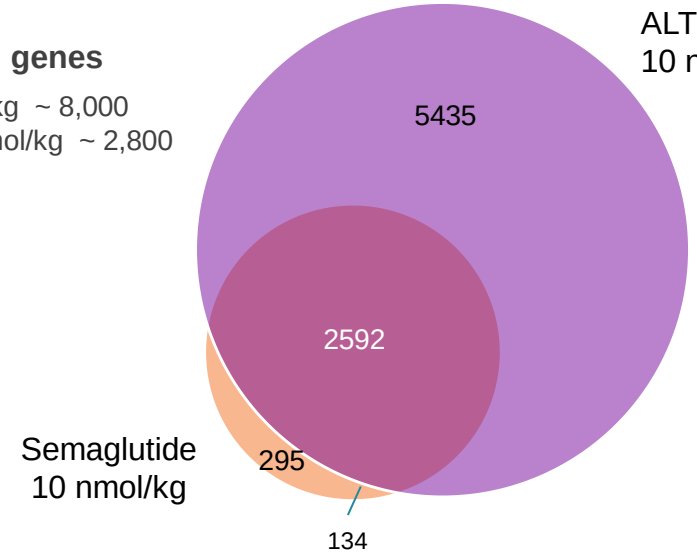
altimmune

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



ALT-801——modulation of genes affecting:
10 nmol/kg

- Fat usage and transport—FASN, GPAT 2,4, PPAR-α,β, SCT-1, CD36
- Pro-fibrosis stellate cell pathways—A-SMA, PDGF-β, TGF-β
- Cell death—AIM2, IPAF, RIPK3
- Inflammation— JUN, FOSB, TLR4

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.

altimmune

GLP-1/GIP DUAL AND TRIPLE RECEPTOR AGONISTS IN DEVELOPMENT

Company	Molecule	Agonists	Status/ Phase	Frequency of Administration	Side Chain	GLP-1R/GCGR/GIP Ratio in vitro	Liver Specific Effects in NASH
Lilly	Tirzepatide (LY3298176)	GLP-1/ GIP Dual Agonist	Phase 3 Diabetes Phase 2 NASH	Weekly	Fatty di-acid	Biased to GIP	No
Novo-Nordisk	NNC0090-2746	GLP-1/ GIP Dual Agonist	Development halted	Daily	fatty-acylated	Balanced	No
Hanmi	HM15211	GLP-1/ GIP/GCCR Triple Agonist	Phase 2 NASH	Weekly	Ig Fc	Not published	Yes

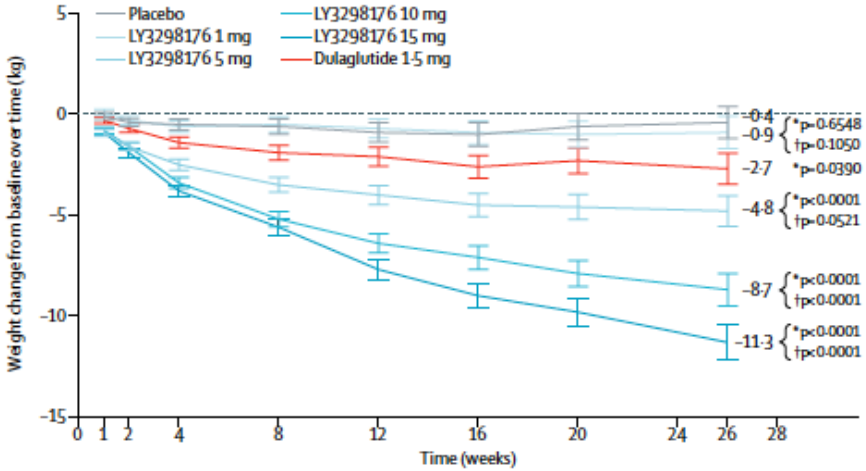
- GIP is a potent stimulator of insulin release and suppressant of gastric emptying
- The effects of GIP on adipose tissue and peripheral energy metabolism are controversial
- Diabetic patients may be desensitized to the effects of GIP on insulin release
- Agents combining GIP with other incretins have demonstrated high degrees of GI side effects

Coskun, Molecular Metabolism 2018; 18: 3e14

altimmune

PHASE 2 TRIAL OF TIRZEPATIDE IN TYPE 2 DIABETES

Weight loss over 26 weeks



High rates of adverse events

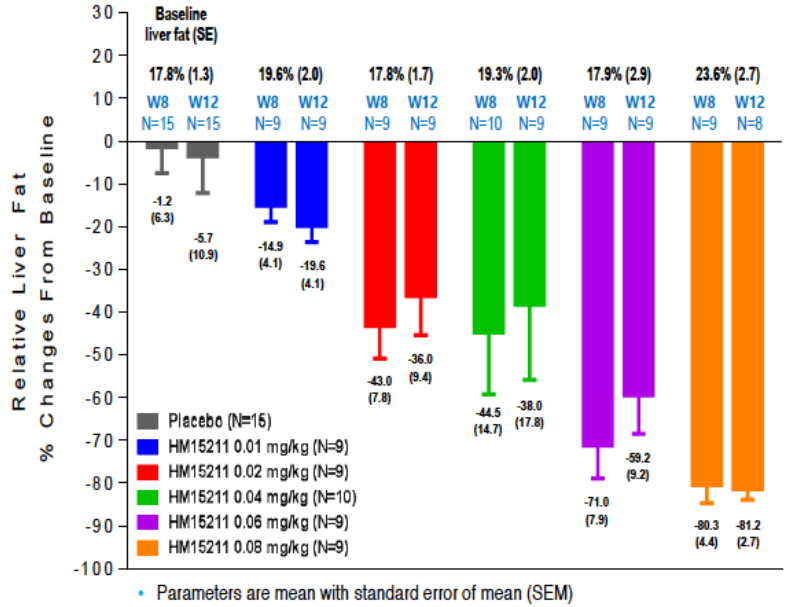
- 66% of patients in the high-dose (15 mg) group had GI adverse events (AEs)
- 24.5% of patients receiving 15 mg had AEs leading to treatment discontinuation
- Attempts to mitigate by extending dose titration beyond 20 weeks in Phase 3

Frias JP, Lancet 2018; 392: 2180–93

altimmune

PHASE 1 12-WEEK TRIAL OF HM15211, A GLP-1/GLCC/GIP TRIPLE AGONIST IN NON-DIABETIC, OBESE SUBJECTS WITH NAFLD

Relative changes in liver fat by MRI-PDFF



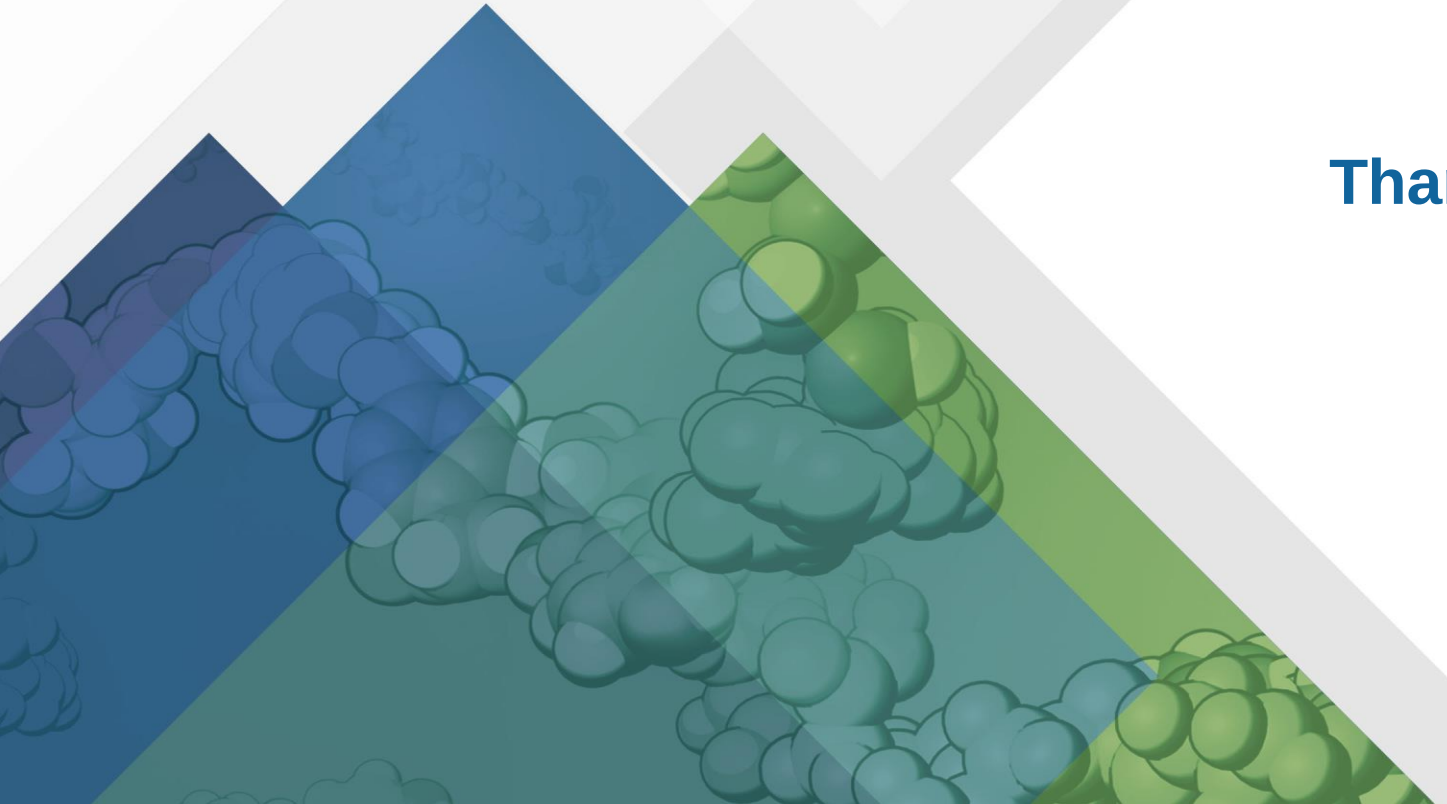
- Only 5% weight loss was realized at the highest (0.08 mg/kg) dose, suggesting that the effects on liver fat reduction were due to glucagon agonism

Abdelmalek, EASL (DILC) 2020

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
- Effective agents should induce pleiotropic effects across multiple pathways involved in NASH pathogenesis
- Glucagon agonism in combination with GLP-1 agonists exhibits synergistic effects on weight loss and liver fat reduction and hold promise for the treatment of both NASH and obesity

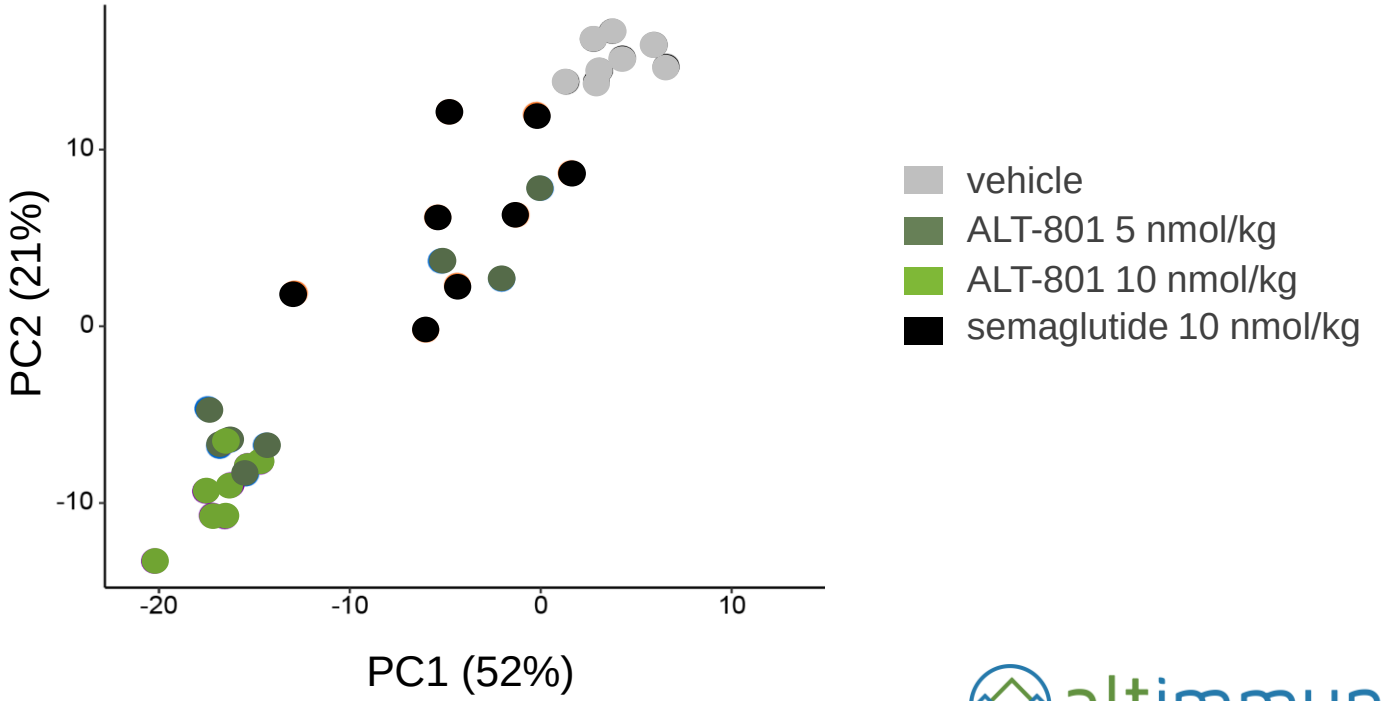
altimmune



Thank You

PLEIOTROPIC EFFECTS

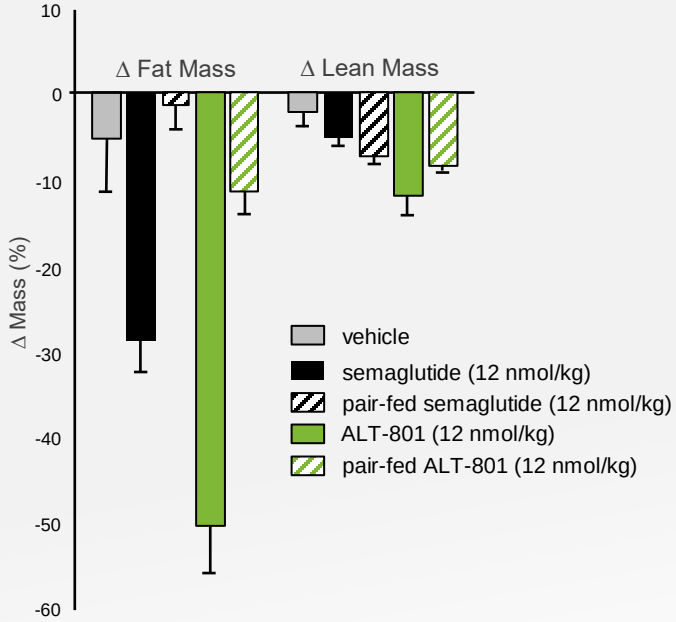
PRINCIPAL COMPONENT ANALYSIS



altimmune

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