Emerging Weight Loss Therapeutics and Implications for the NASH Treatment Paradigm

M. Scott Harris, MD
Chief Medical Officer
Altimmune, Inc.

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Forward-looking statements

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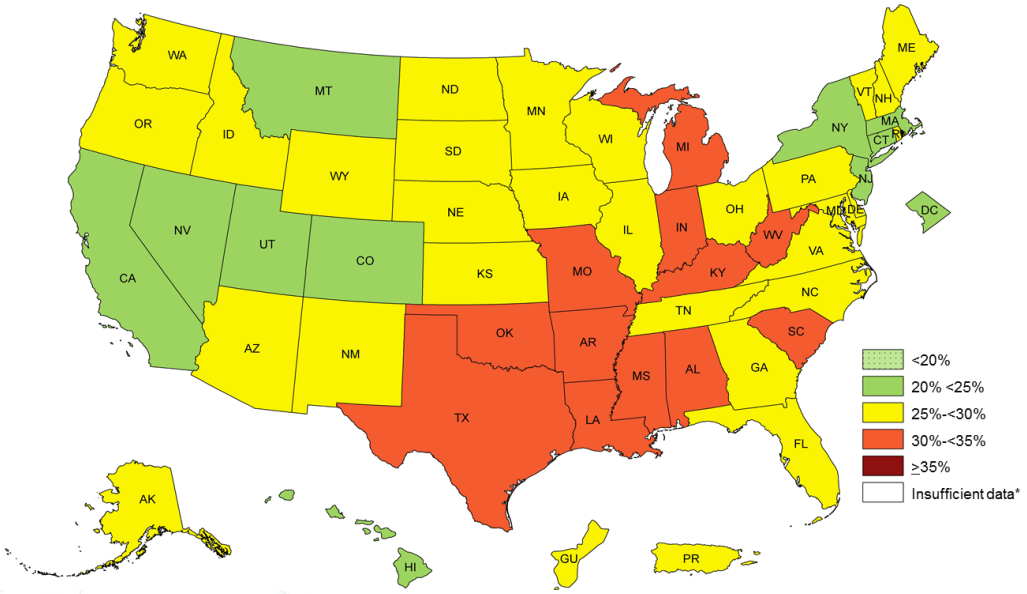
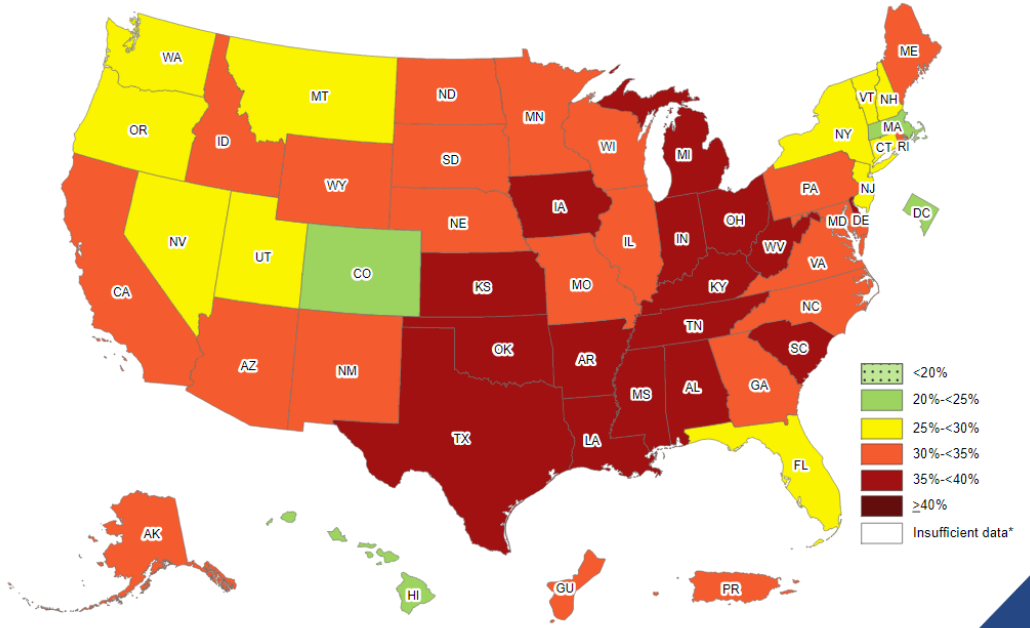
CDC: OBESITY IN U.S. DRAMATICALLY INCREASING

PREVALENCE OF SELF-REPORTED OBESITY AMONG U.S. ADULTS BY STATE AND TERRITORY[1]

2011



2020



1 - https://www.cdc.gov/obesity/data/prevalence-maps.html#race

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OBESITY: SIGNIFICANT BURDEN TO HEALTHCARE SYSTEM

OPPORTUNITY TO ADDRESS MANY COMORBIDITIES THROUGH THE TREATMENT OF OBESITY

IMPACT OF OBESITY

- Obesity is implicated in **two thirds of the leading causes of death** from non-communicable diseases worldwide[1]
- Total obesity related medical care in the U.S. estimated to be **$147 billion** per CDC[2]
- Global market size for medical weight loss alone was **$8.36 billion** in 2020, and is estimated to reach **$27.1 billion** by 2028[3]

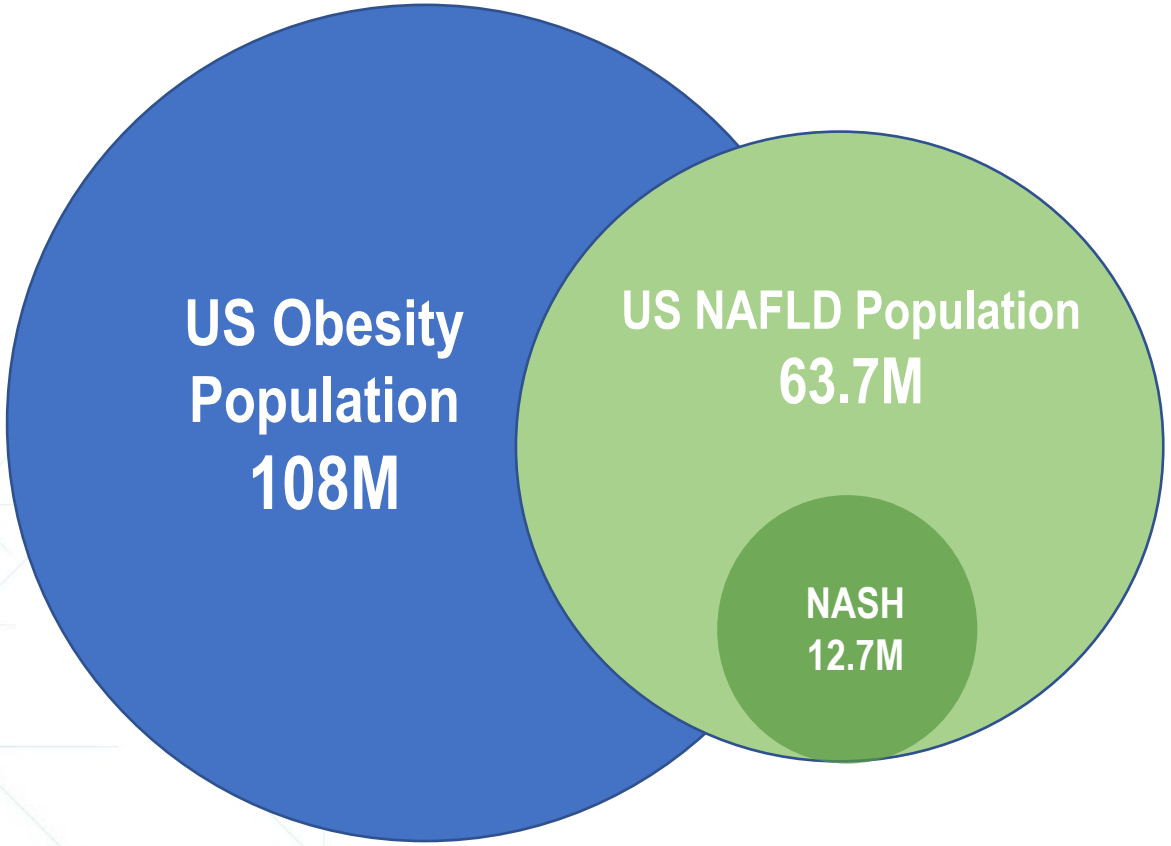
COMORBIDITIES

- High blood pressure
- High cholesterol
- Type 2 diabetes
- Coronary heart disease
- Stroke
- Gallbladder disease
- Osteoarthritis
- Sleep apnea and breathing problems
- Certain cancers
- NASH

1 - https://www.sciencedaily.com/releases/2019/10/191024143218.htm
2 - https://www.cdc.gov/obesity/adult/causes.html
3 - https://www.biospace.com/article/obesity-treatment-market-size-to-reach-usd-27-10-billion-in-2028/

OBESITY AND FATTY LIVER DISEASE

DISEASES WITH UNMET NEED APPROACHING EPIDEMIC PROPORTION



- The treatment of obesity is the cornerstone of treating NASH and the principal co-morbidities of NASH[1,2]
- Previous approaches to the treatment of obesity have been associated with safety concerns limiting success
- The recent success of semaglutide (Wegovy™) has created a regulatory pathway for other incretin-based approaches

[1]Glass LM, Fed Pract 2019; [2]Perazzo H, Liver Int 2017

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DEATHS IN NAFLD: COMPLICATIONS OF OBESITY

LIVER DISEASE ACCOUNTS FOR ONLY A MINORITY OF DEATHS

Outcome	n (%)
Death or liver transplantation	193 (100.0)
Cardiovascular disease	74 (38.3)
Non-liver cancer	36 (18.7)
Cirrhosis complications	15 (7.8)
Infections	15 (7.8)
HCC	2 (1)
Liver transplantation	1 (0.5)
Other	35 (18.1)
Unknown	15 (7.8)

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

WEIGHT LOSS AND IMPROVEMENT OF OBESITY COMPLICATIONS

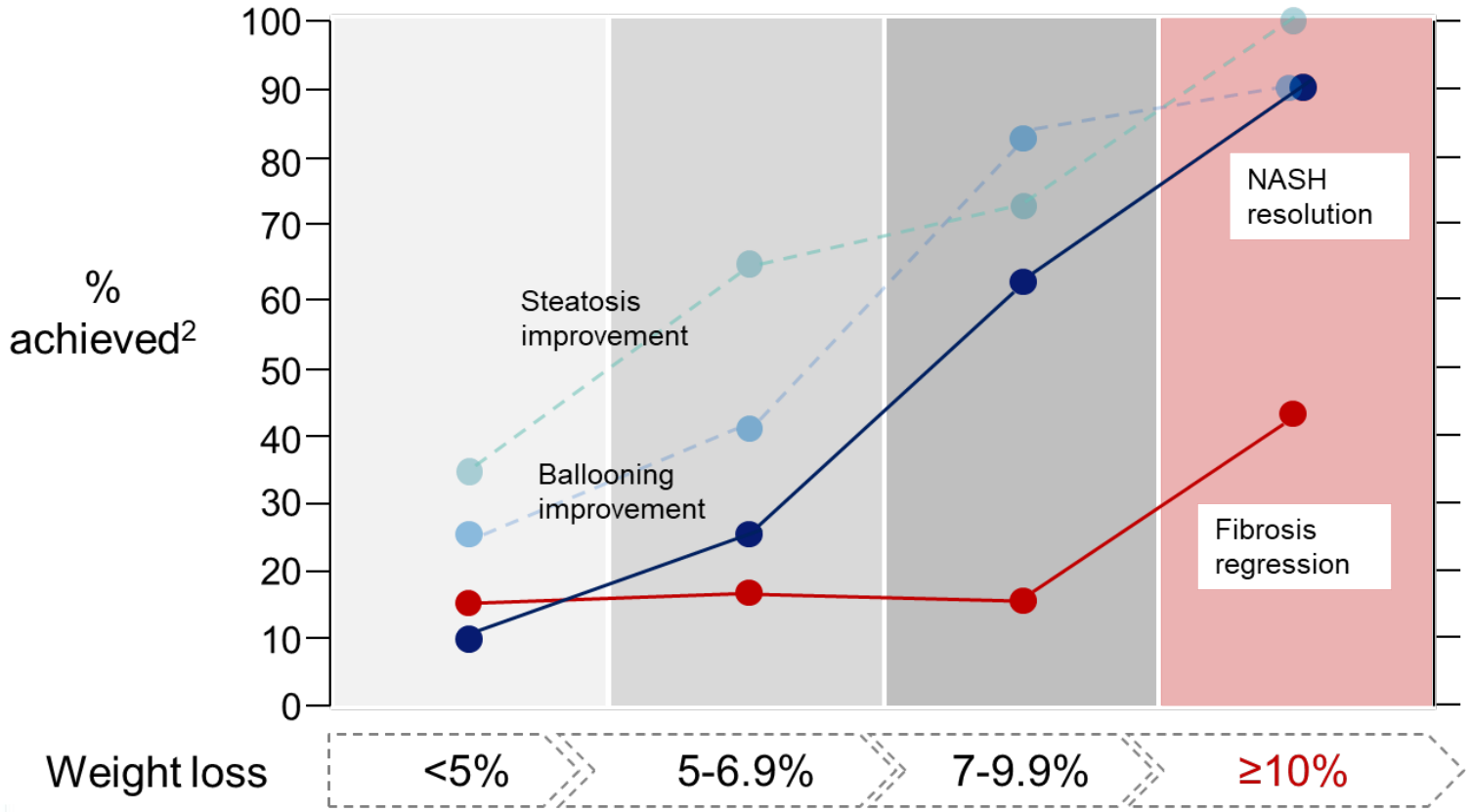
AN EFFECTIVE THERAPY WOULD ACHIEVE AT LEAST 10% WEIGHT LOSS

Complication	Weight Loss Target (%)
NASH	10
Type 2 diabetes	5-15
Hyperlipidemia	10-15
Hypertension	15
Osteoarthritis	5-15
Sleep apnea	10
Gastroesophageal reflux	10-15
Stress incontinence	10

Adapted from Cefalu, Diabetes Care 2015

TREATING OBESITY IS THE CORNERSTONE OF NASH THERAPY

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



[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*

[2] *Adapted from Harrison, EASL 2019, Traber, Discovery on Target: Targeting NASH 2019, and Vilar-Gomez, Gastroenterology 2015*

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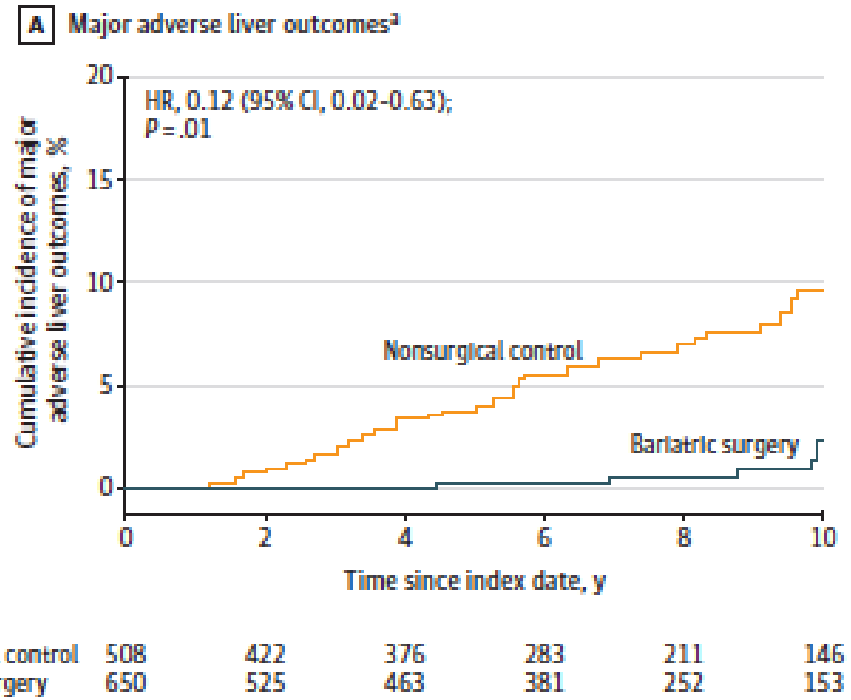
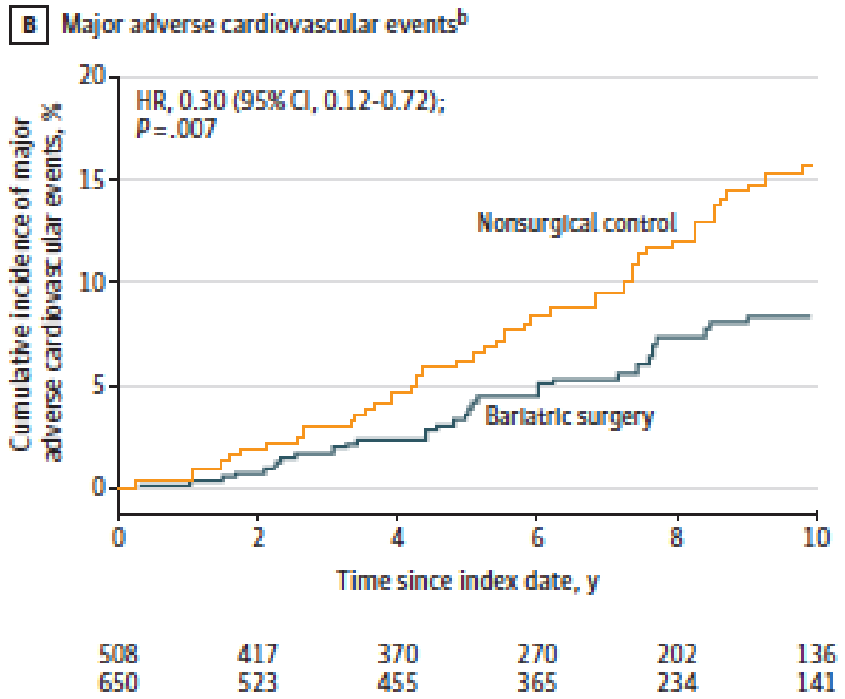
BARIATRIC SURGERY IMPROVES NASH OUTCOMES

LOWERS ADVERSE LIVER OUTCOMES AND MAJOR ADVERSE CARDIOVASCULAR EVENTS





Aminian, JAMA 2021

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MOST NASH AGENTS FAIL TO ACHIEVE MEANINGFUL WEIGHT LOSS

SNAPSHOT OF COMPOUNDS IN ADVANCED NASH DEVELOPMENT

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; 3.7%†††
Firsocostat	Lawitz, EJ 2018[6]	ACC inhibitor	no change
Lanifibranor (1200 mg)	Franque, S 2020[7]	PanPPAR	increases 3.1%

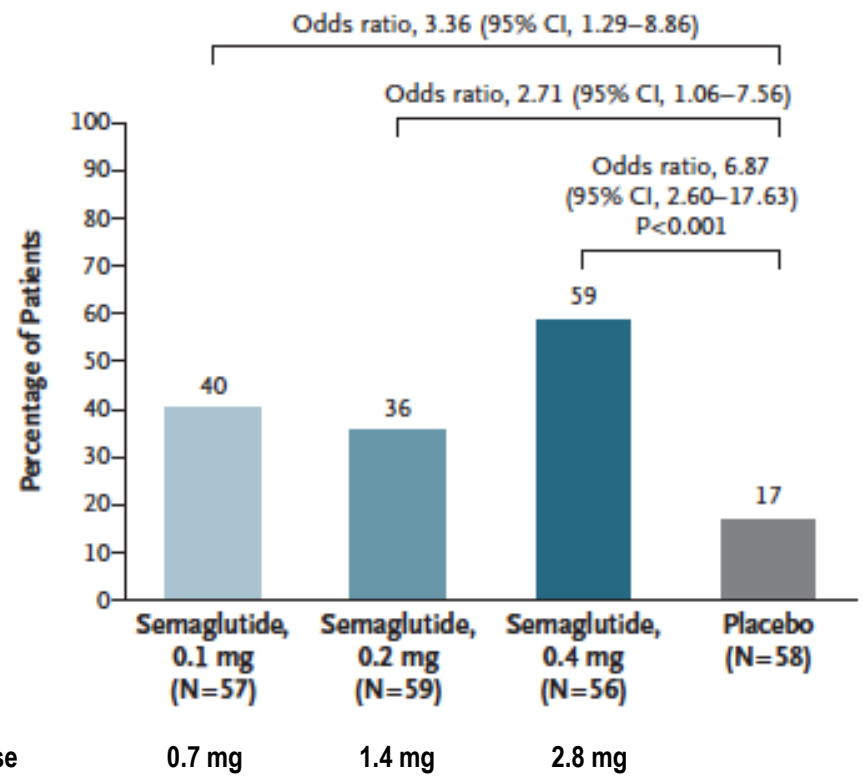
† No information has been made public on 1mg dose
†† Gain of 0.6% on 20mg dose
††† BALANCED study (June 30 corporate deck)

[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

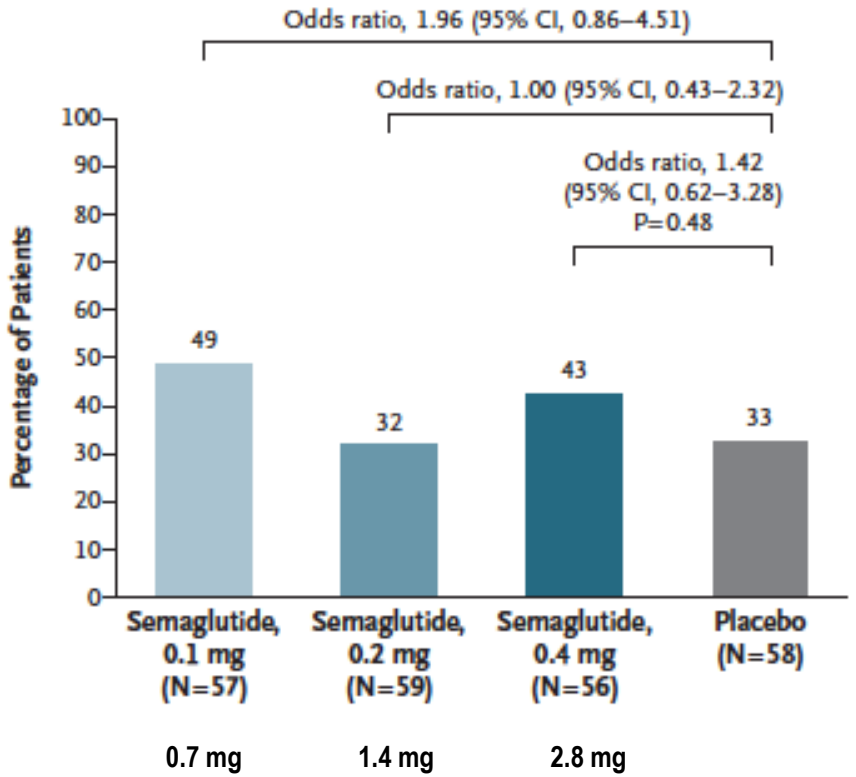
SEMAGLUTIDE—NASH RESOLUTION WITHOUT FIBROSIS IMPROVEMENT

RESULTS OF A 68-WEEK, PHASE 2, MULTICENTER TRIAL

NASH Resolution



Fibrosis Improvement



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

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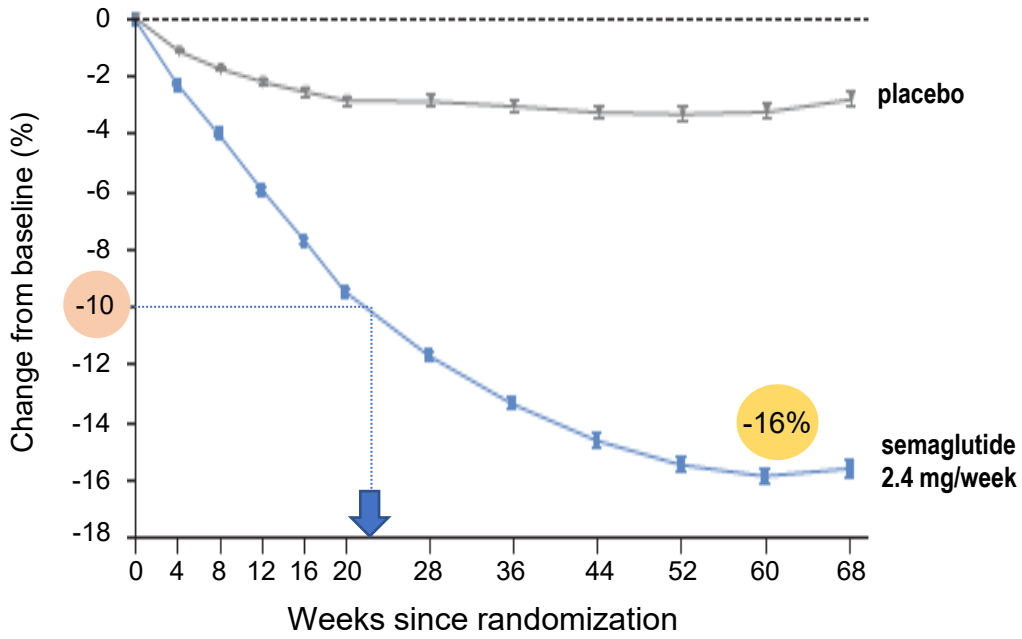
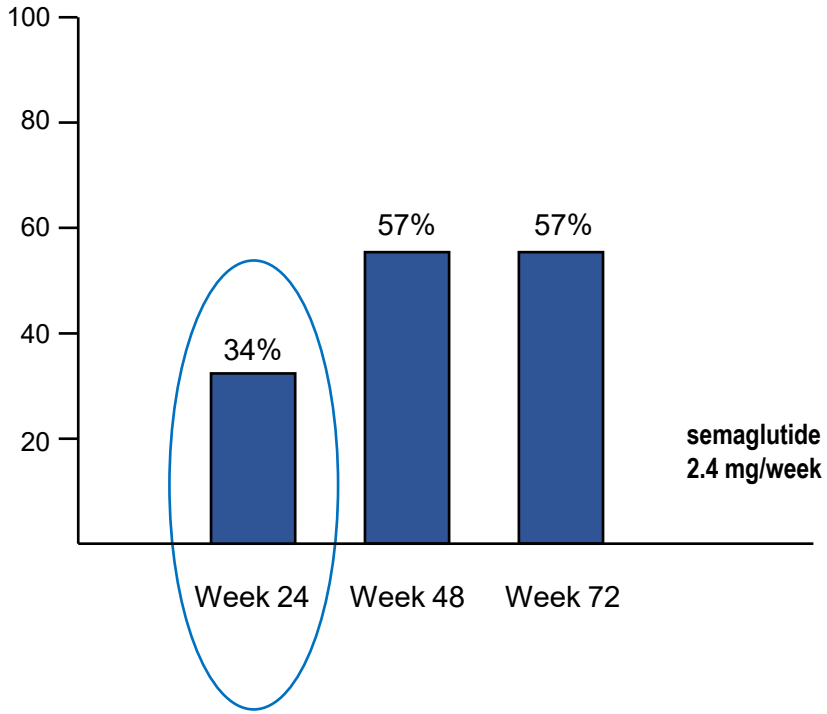
SEMAGLUTIDE—DELAYED REDUCTIONS IN BODY WEIGHT AND LIVER FAT

FIBROSIS IMPROVEMENT MAY NOT HAVE BEEN REALIZED WITHIN TREATMENT PERIOD

Body weight, % change from baseline



LFC, relative reduction (%), estimated at 24, 48 and 72 weeks



Adapted from Wilding, STEP 1 trial, NEJM 2021, and Flint, Aliment Pharm Ther 2021

LFC, liver fat content

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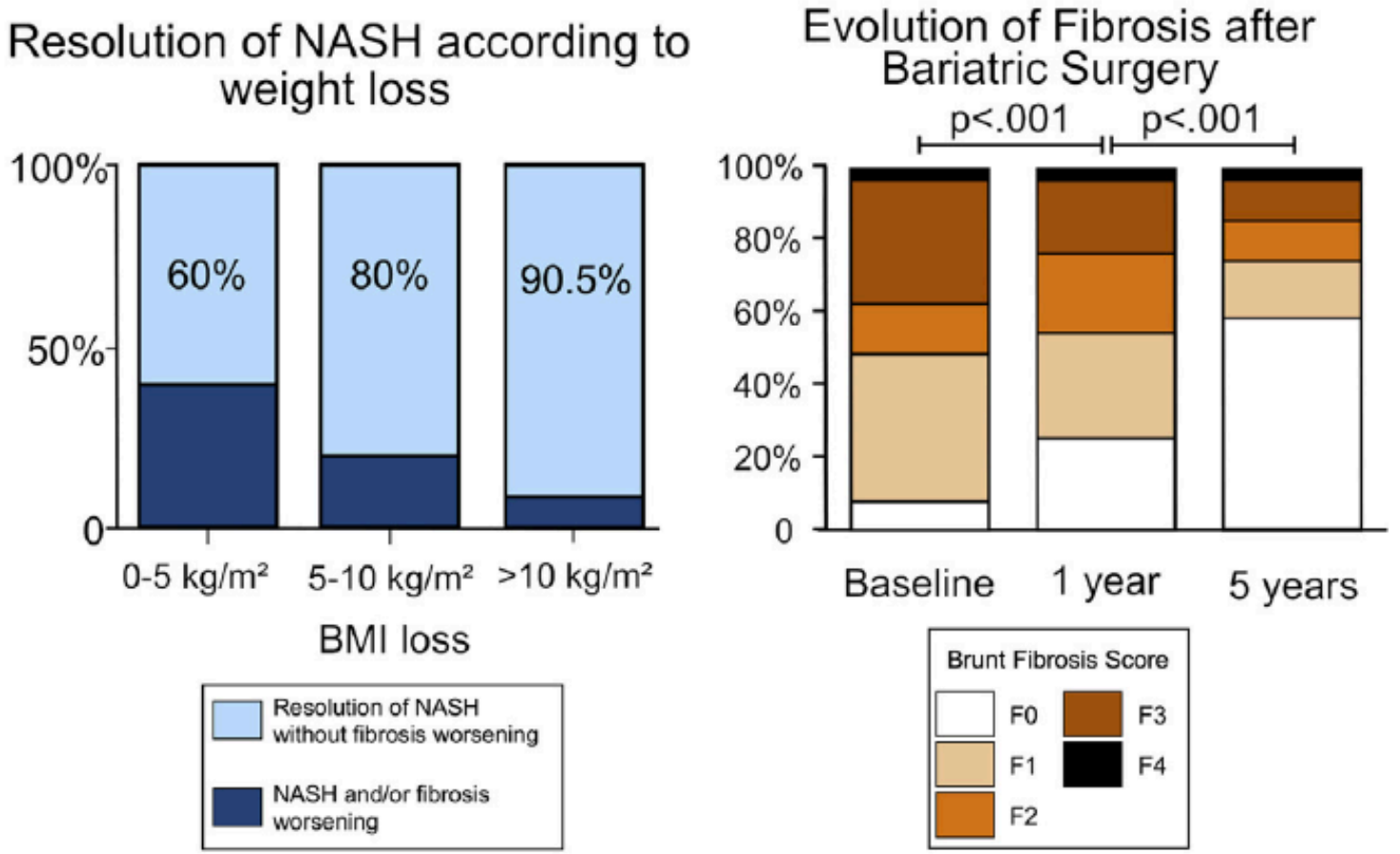
BARIATRIC SURGERY IS A POTENT NASH THERAPY

BUT THE TIME COURSE FOR FIBROSIS IMPROVEMENT DUE TO WEIGHT LOSS ALONE MAY BE EXTENDED



Lassailly Gastroenterology 2020

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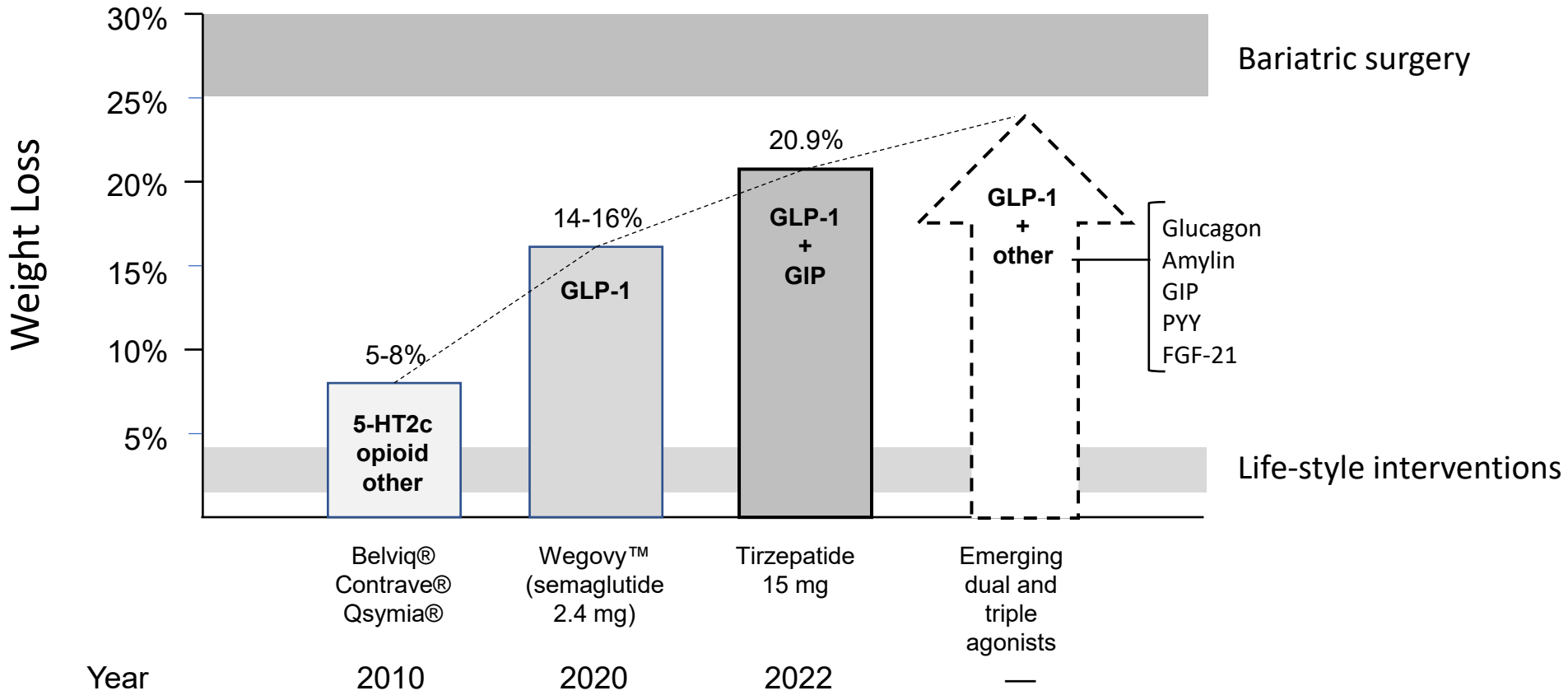
EMERGING THERAPIES DRAW CLOSER TO THE WEIGHT LOSS ACHIEVED BY BARIATRIC SURGERY



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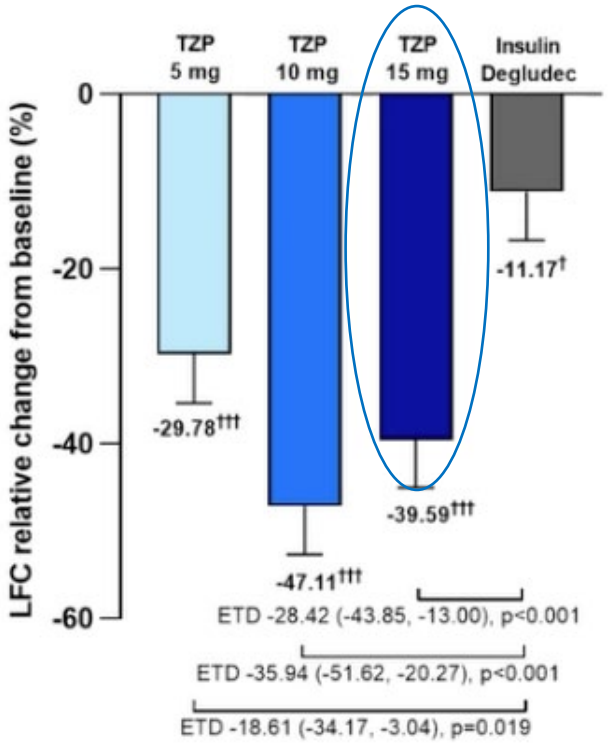
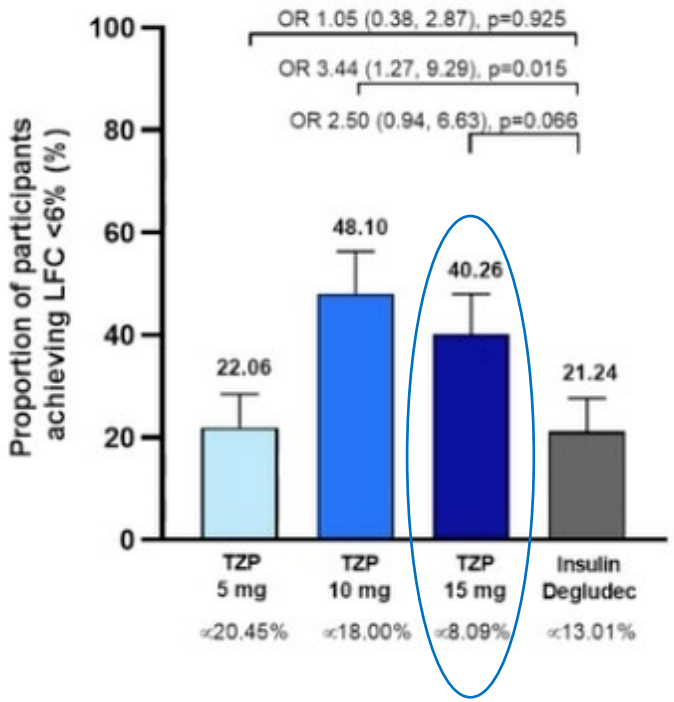
TIRZEPATIDE (GLP-1/GIP) — LOW TO MODERATE REDUCTION IN LFC

ABSENCE OF DIRECT EFFECTS OF GLP-1 AND GIP ON LIVER

LFC, relative reduction (%) at 52 weeks



LFC, proportion of subjects achieving < 6% at 52 weeks



LFC, liver fat content

Haupt, 5th NASH Summit, SURPASS 3 Trial, November 2021

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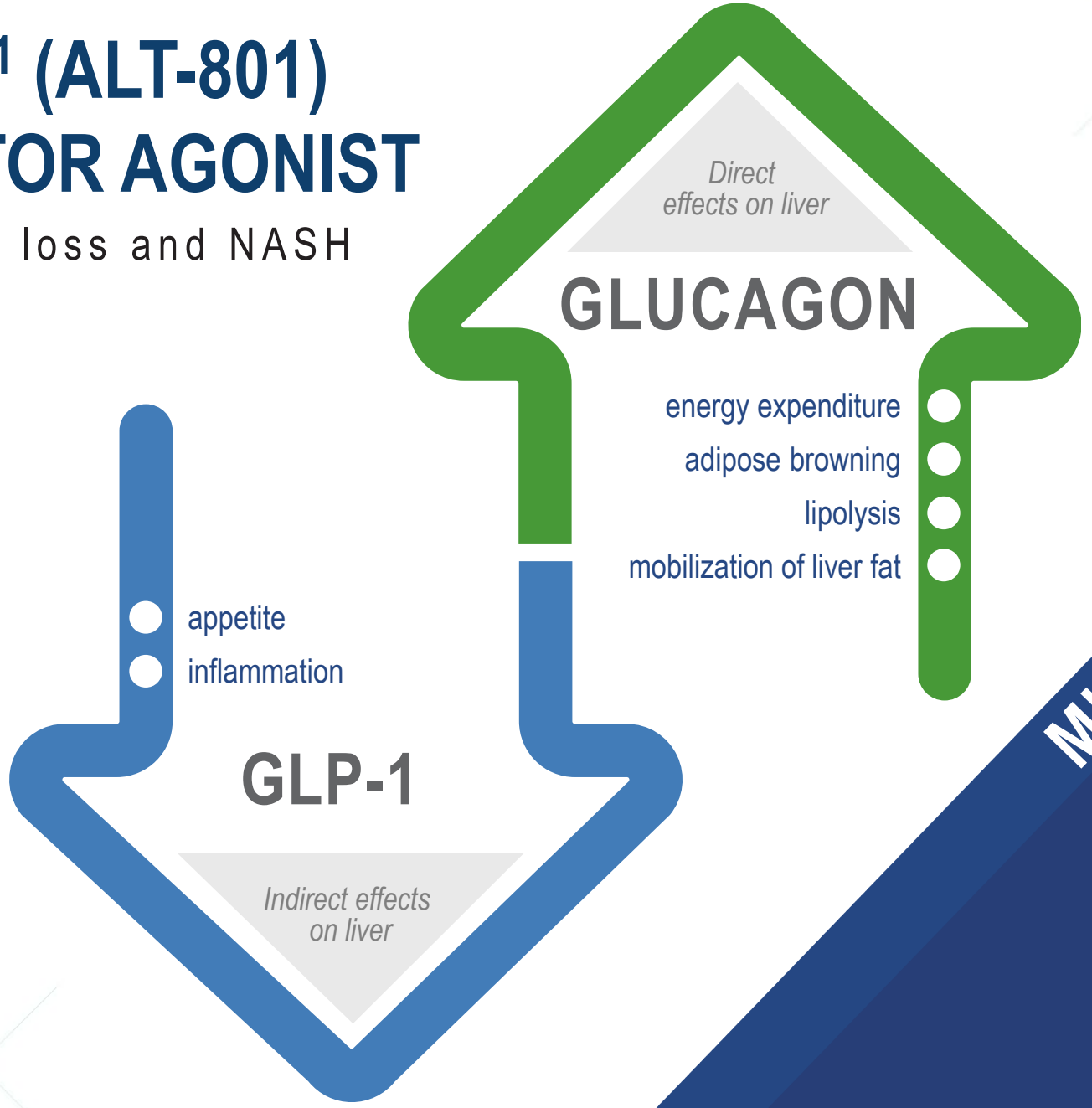
PEMVIDUTIDE[1] (ALT-801)
DUAL RECEPTOR AGONIST

Optimized for weight loss and NASH

Designed for significant reductions in:

BODY WEIGHT

LIVER FAT, INFLAMMATION, & RESULTING FIBROSIS



MIMICS

[1] proposed INN

PEMVIDUTIDE (ALT-801)

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

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

EuPort™ domain
Weekly dosing, improved PK for improved GI tolerability

Glucagon specificity
Improved weight loss

GLP-1 specificity
Restores metabolic function

Modified residue
Protease stability

Helix Stabilizer
Increased potency[2]

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

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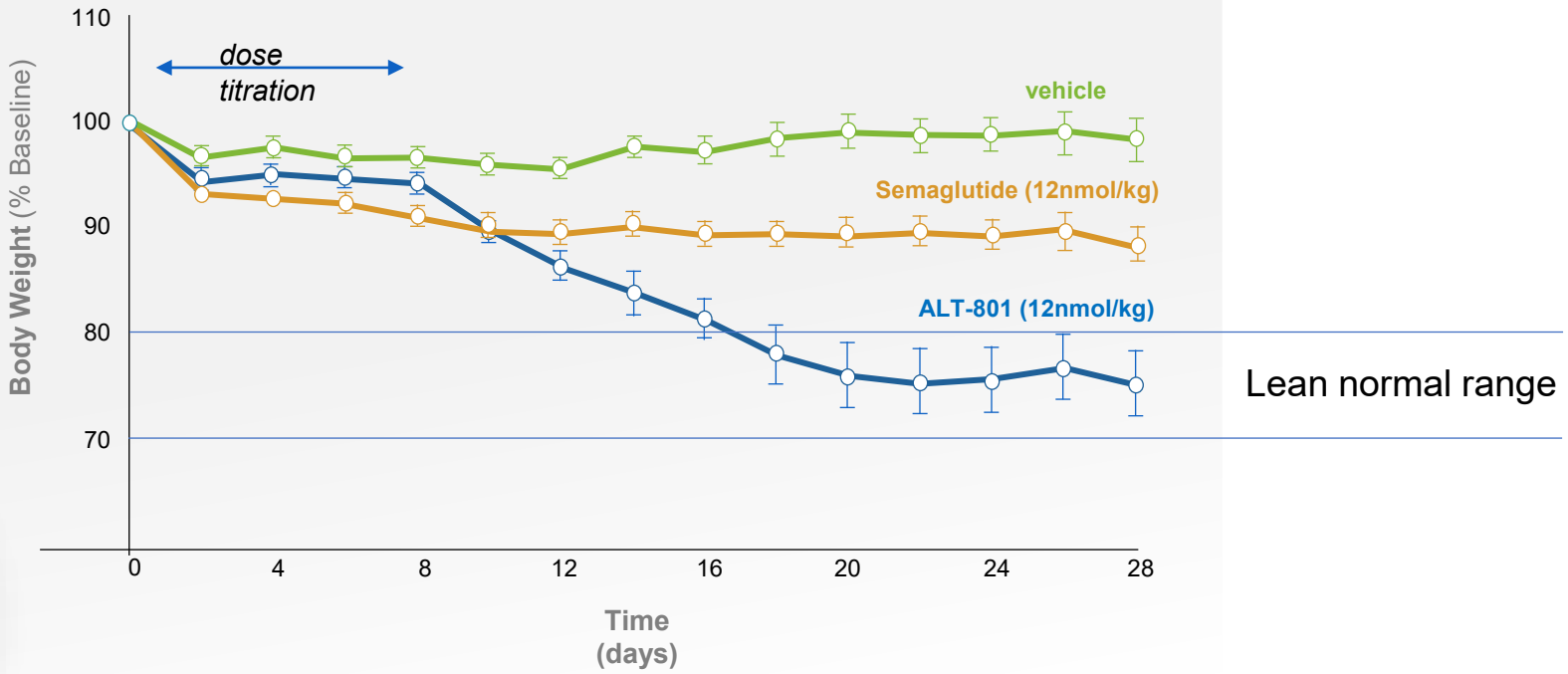
PEMVIDUTIDE (ALT-801) IN MOUSE DIET-INDUCED OBESITY (DIO) MODEL

2-FOLD GREATER WEIGHT REDUCTION THAN GLP-1 MONOTHERAPY AND TO LEAN NORMAL RANGE

Mouse DIO Model After 4 Weeks of Treatment



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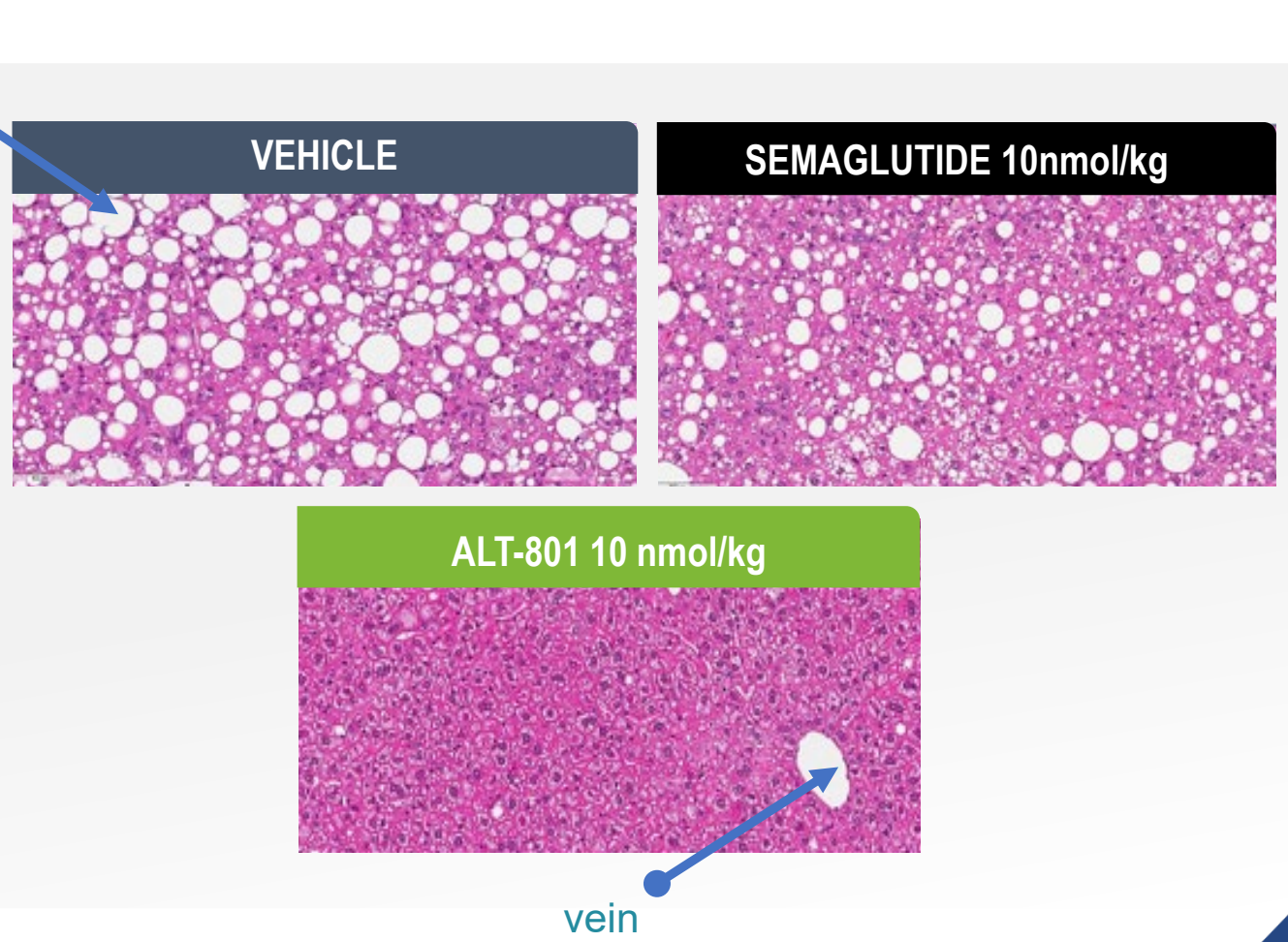
PEMVIDUTIDE (ALT-801) IN GUBRA MOUSE MODEL OF NASH

SUPERIOR EFFECTS VS GLP-1 MONOTHERAPY—LIVER FAT REDUCED TO ALMOST UNDETECTABLE LEVELS

Gubra Model After 12 Weeks of Treatment



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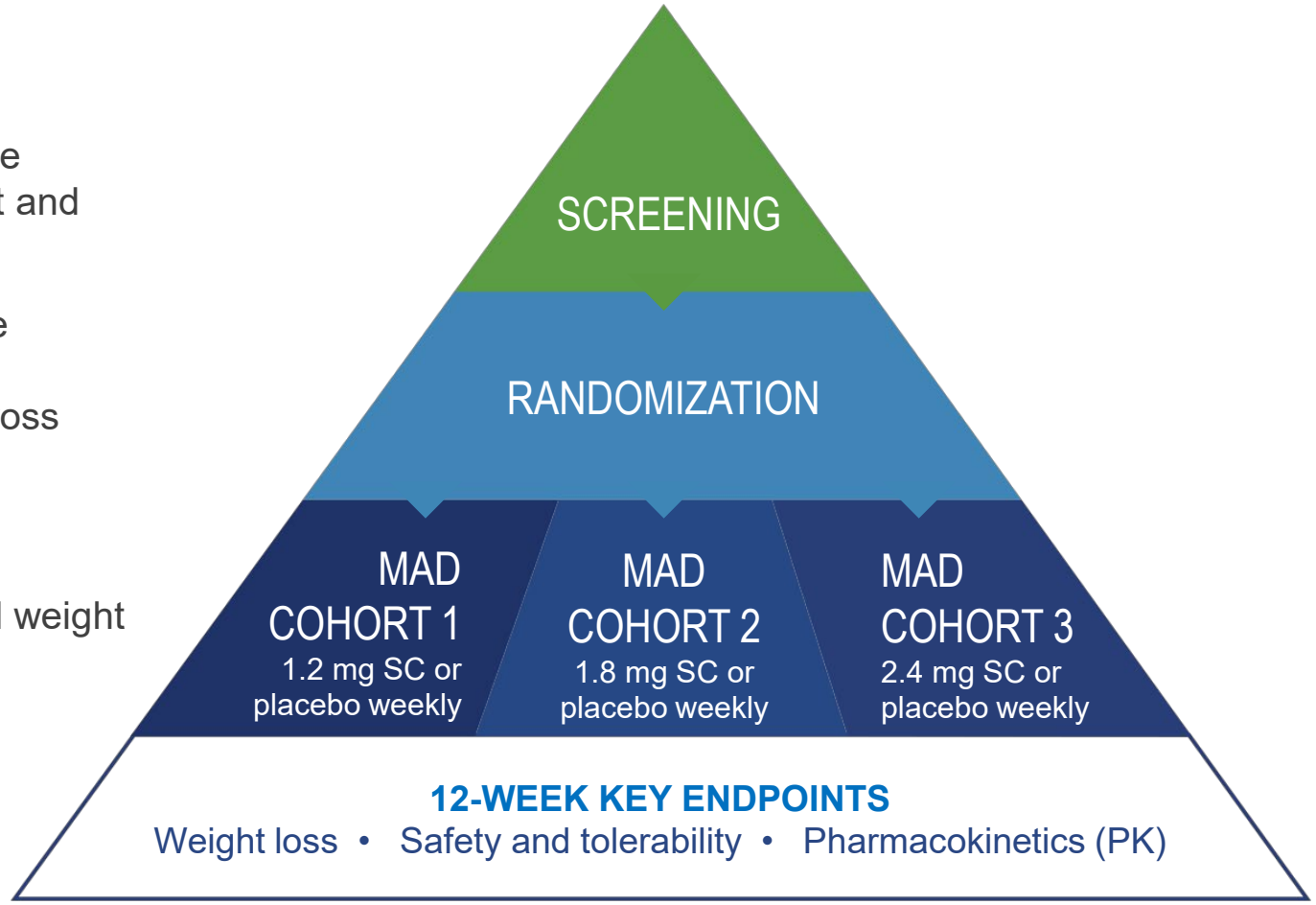
PEMVIDUTIDE PHASE 1— MAD TRIAL DESIGN

- Phase 1, first-in-human, placebo-controlled, multiple ascending dose (MAD) study in healthy overweight and obese volunteers
- Within MAD cohorts, patients were randomized 4:1 to pemvidutide or placebo, with placebos pooled across cohorts
- **No dose titration**
- No calorie restriction or behavioral weight loss programs



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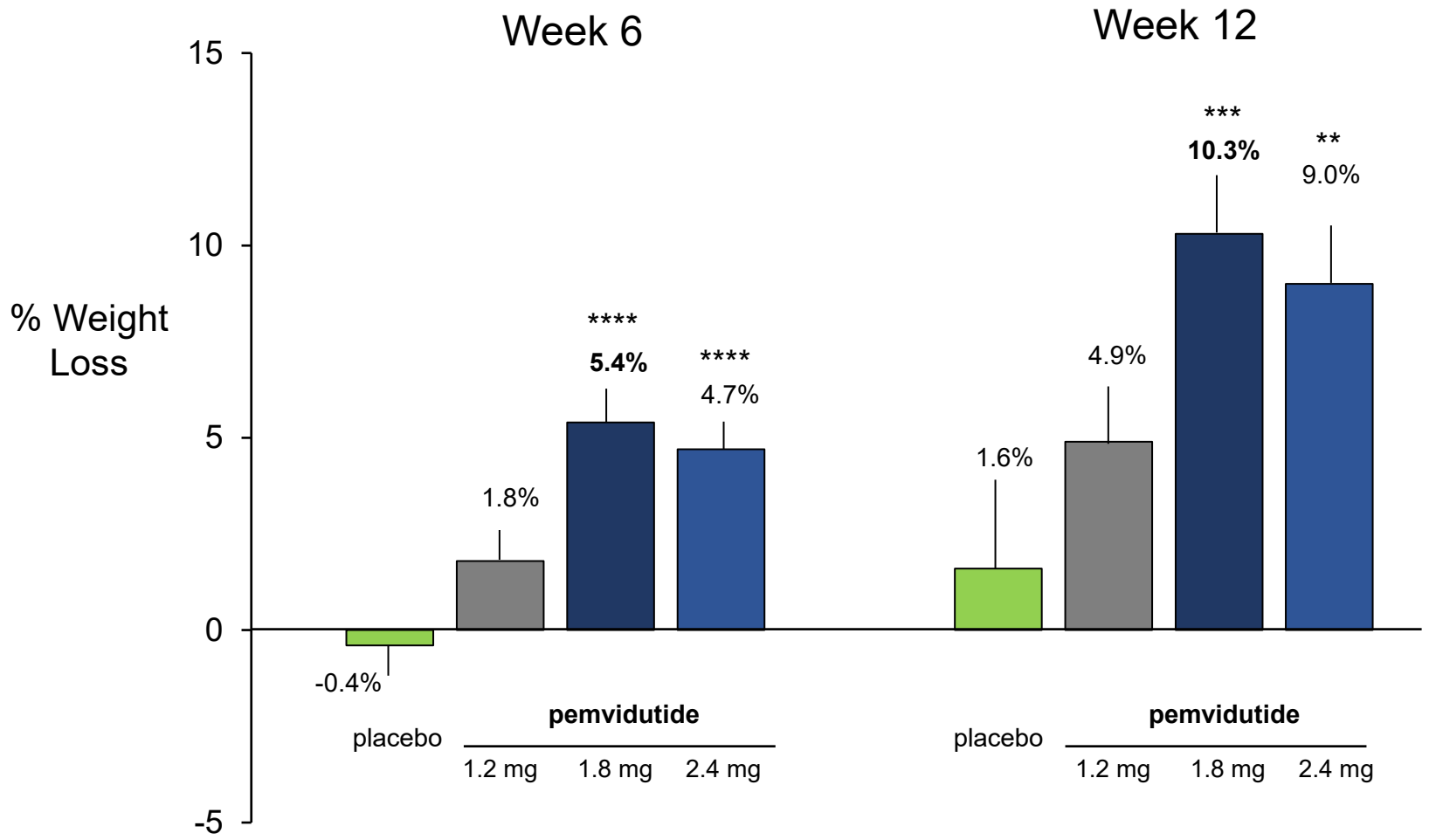
PEMVIDUTIDE PK PROFILE CONFIRMS WEEKLY DOSING

LOWER C_{max} AND DELAYED T_{max} MAY ENHANCE TOLERABILITY

PK PARAMETER	ALT-801 1.8 mg SC
Peak concentration (C_{max})	27.1 nmol/L
Area under curve (AUC) $_{0\text{-}168}$	3400 nmol•hr
Half-life ($t_{1/2}$)	110 hrs
Time to peak concentration (T_{max})	70 hrs

ROBUST WEIGHT LOSS AT WEEK 12

10.3% MEAN WEIGHT LOSS ACHIEVED AT 1.8 MG DOSE



*** p < .01, ***p < .005, ****p < .001; compared to placebo*

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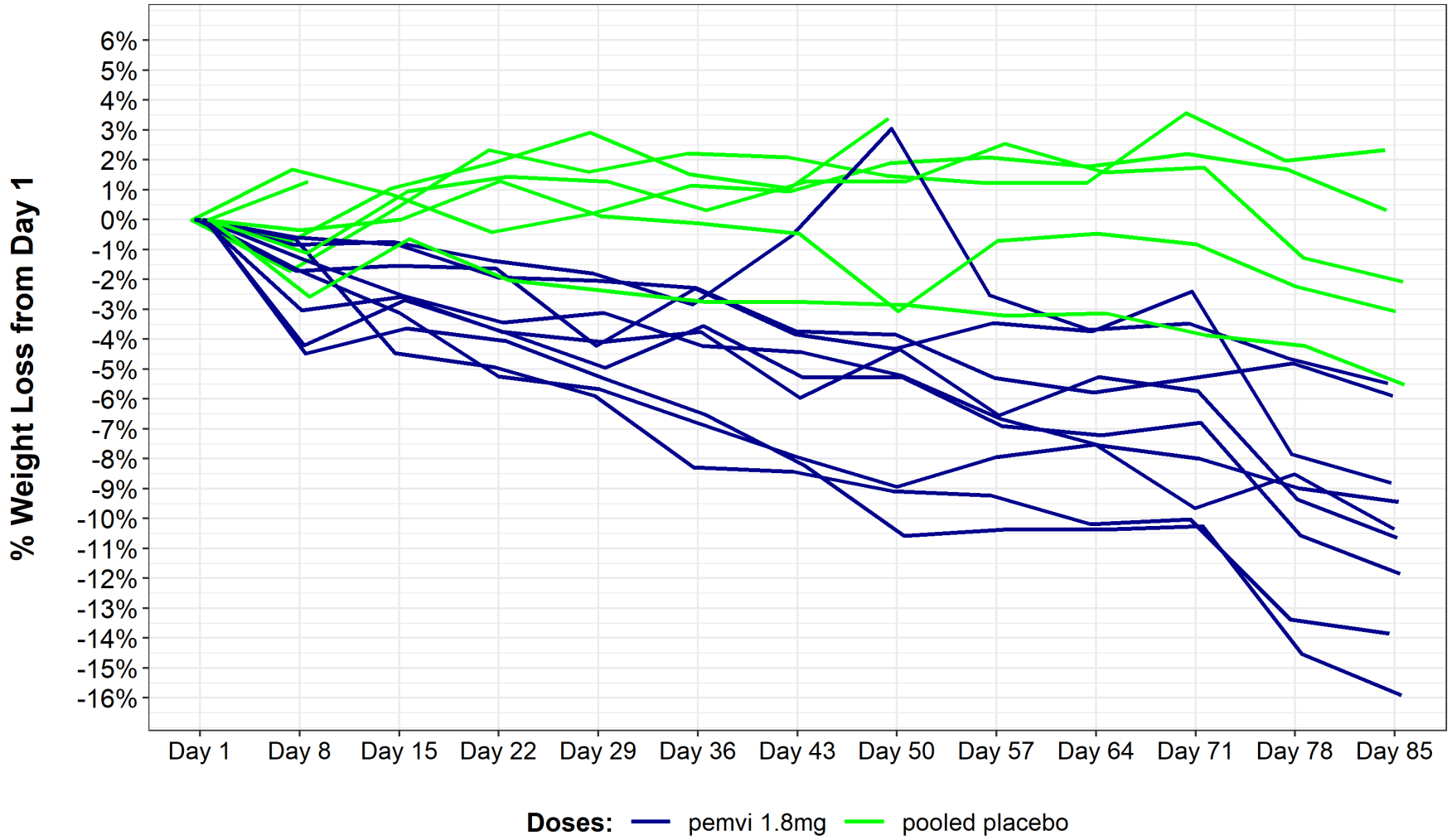
MAJORITY OF SUBJECTS AT 1.8 MG DOSE ACHIEVED 10% OR MORE WEIGHT LOSS AT WEEK 12



- 55% of subjects achieved 10% or more weight loss by Week 12
- 100% of subjects achieved 5% or more weight loss by Week 12

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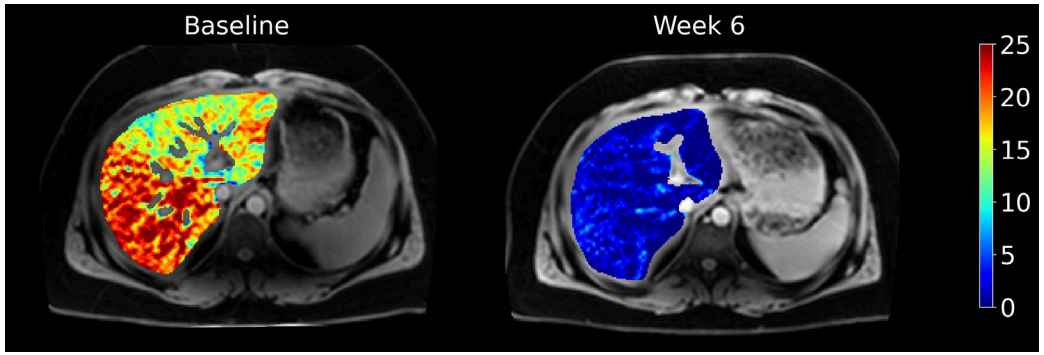
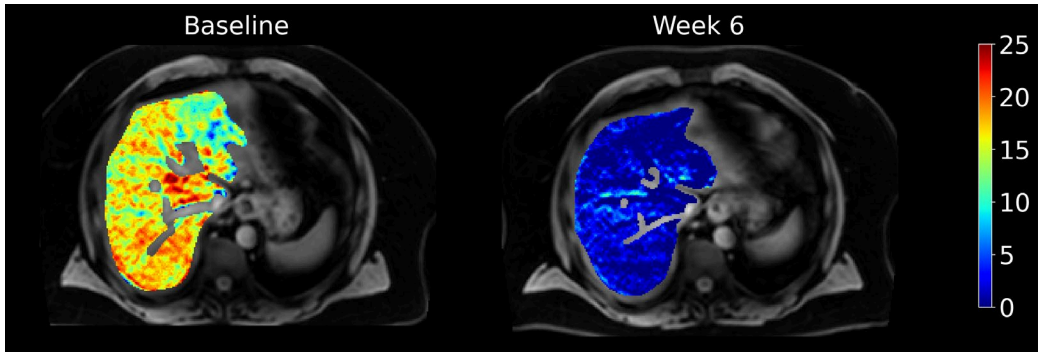
GREATER THAN 90% REDUCTION IN LIVER FAT BY MRI-PDFF IN 6 WEEKS

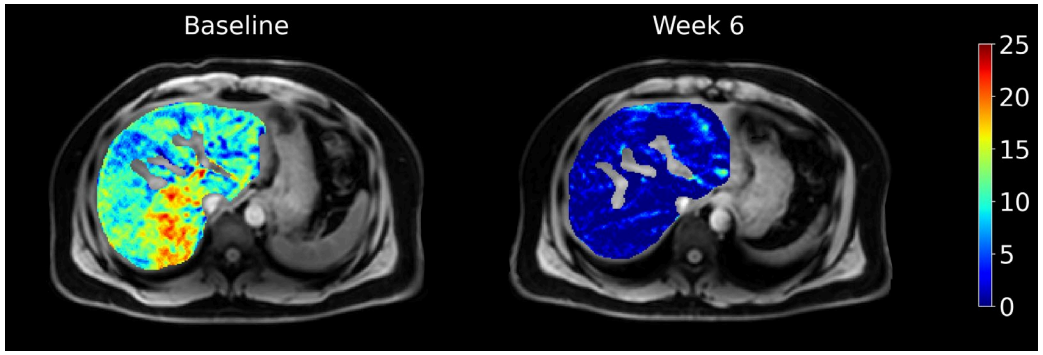
PEMVIDUTIDE DECREASED LFC TO UNDETECTABLE LEVELS AT THE 1.8 MG AND 2.4 MG DOSES



19.5% **Below LOD**



17.0% **Below LOD**



12.5% **Below LOD**

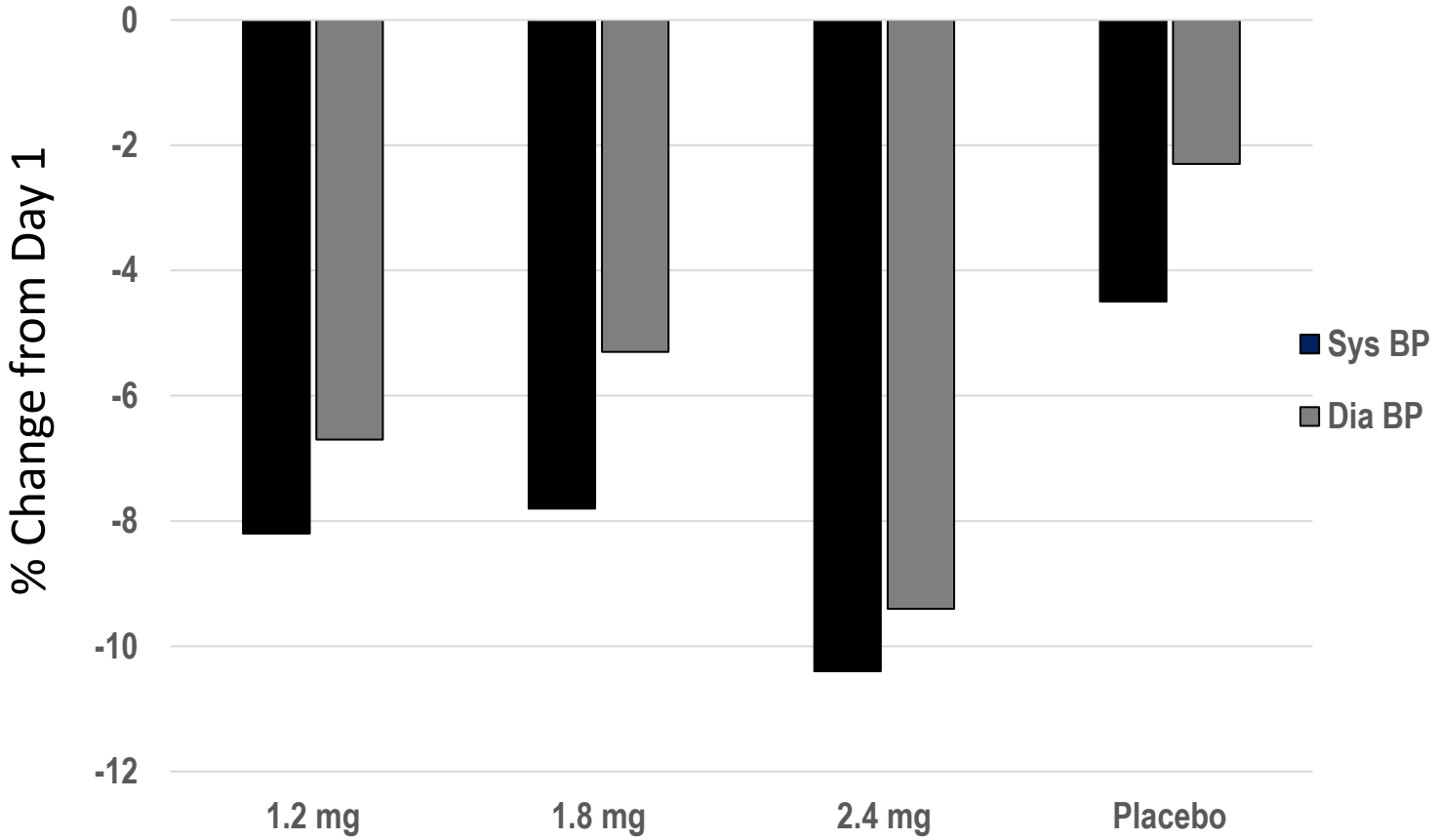
Exploratory analysis of subjects with baseline LFC ≥ 5%

- All subjects receiving pemvidutide 1.8 or 2.4 mg achieved undetectable levels of liver fat by MRI-PDFF at Week 6 – a greater than 90% reduction
- Potentially a new standard in NASH treatment for the speed and magnitude of liver fat effects

LFC, liver fat content; LOD, Limit of Detection

CHANGE IN BLOOD PRESSURE OVER 12 WEEKS OF TREATMENT

NO CHANGES IN HEART RATE OBSERVED ACROSS DOSES



Means of weekly measurements, Weeks 1-12, compared to Baseline

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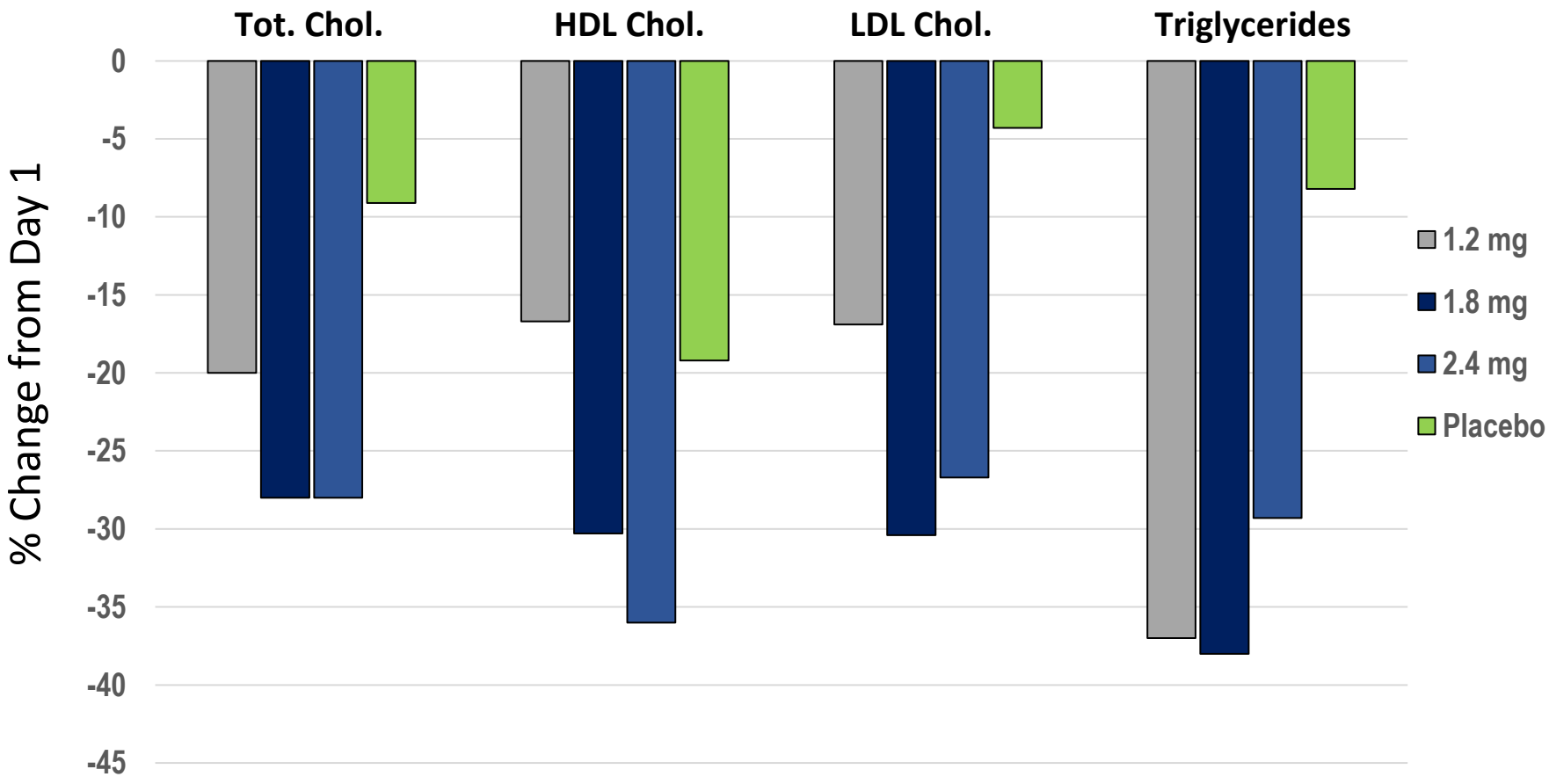
IMPORTANT REDUCTION SERUM LIPIDS AT WEEK 12

REDUCTIONS OCCURRED IN ALL MAJOR LIPIDS CLASSES



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GLUCOSE HOMEOSTASIS MAINTAINED

Characteristic		Treatment			
		1.2 mg	1.8 mg	2.4 mg	Pooled placebo
Fasting Serum Glucose (FSG) [1]					
Change from Baseline	mg/dL (%)	3.0 (3.5%)	-0.4 (-0.5%)	-0.8 (-0.9%)	-0.2 (-0.2%)
HbA1c (%)					
Baseline	mean (SD)	5.3 (0.1)	5.5 (0.2)	5.3 (0.2)	5.3 (0.2)
Week 12	mean (SD)	5.4 (0.2)	5.4 (0.3)	5.3 (0.3)	5.3 (0.3)
HOMA-IR (insulin resistance)					
Baseline	mean (SD)	2.5 (1.2)	2.4 (2.5)	3.1 (1.8)	2.4 (1.7)
Week 12	mean (SD)	2.0 (1.4)	2.2 (2.5)	2.4 (1.2)	2.4 (1.2)

[1] *mean of weekly measurements, Weeks 1-12, compared to Baseline*

SAFETY OVERVIEW

NO STUDY DISCONTINUATIONS DUE TO ADVERSE EVENTS

Characteristic		Treatment			
		1.2 mg	1.8 mg	2.4 mg	Pooled placebo
AEs leading to discontinuation	**n (%)**	**0 (%)**	**0 (%)**	**0 (%)**	**0 (%)**
Serious or severe AEs	**n (%)**	**0 (%)**	**0 (%)**	**0 (%)**	**0 (%)**
Nausea					
Mild	n (%)	1 (14.3%)	5 (55.6%)	5 (45.5%)	1 (14.3%)
Moderate	n (%)	1 (14.3%)	1 (11.1%)	5 (45.5%)	0 (0.0%)
Vomiting					
Mild	n (%)	1 (14.3%)	1 (11.1%)	5 (45.5%)	1 (14.3%)
Moderate	n (%)	0 (0.0%)	1 (11.1%)	3 (27.3%)	0 (0.0%)
Diarrhea					
Mild	n (%)	0 (0.0%)	0 (0.0%)	2 (18.2%)	0 (0.0%)
Moderate	n (%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Constipation					
Mild	n (%)	0 (0.0%)	1 (11.1%)	2 (18.2%)	0 (0.0%)
Moderate	n (%)	0 (0.0%)	1 (11.1%)	1 (9.1%)	0 (0.0%)
Hyperglycemia	n (%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)

1 subject receiving 1.8 mg dose and 1 subject receiving placebo experienced 3-5X alanine aminotransferase (ALT) elevations during treatment

Gastrointestinal Adverse Events

- Most frequently mild at 1.8 mg dose with on-drug resolution and not requiring treatment
- No study discontinuations due to AEs

SUMMARY

- Medications are needed that deliver the weight loss of bariatric surgery
- Balanced (1:1) GLP-1/glucagon dual receptor agonism provides faster and greater reductions in body weight and LFC than GLP-1 monotherapy
  - 10.3% weight loss in only 12 weeks
  - Reduction of LFC to below detectable levels in 100% of individuals at 1.8 mg and 2.4 mg
  - Glucose control is maintained
- Agents that can be administered without dose titration are attractive options as weight loss moves into primary care
  - Tolerability can be enhanced by altering PK (increasing T_{max} and lowering C_{max}) and shifting from GLP-1 to glucagon agonism to achieve weight loss and LFC targets

THANK YOU

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NASDAQ: ALT