Role of Glucagon-Containing Dual and Triple Agonists in the Treatment of Obesity and MASH

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Forward-looking statements

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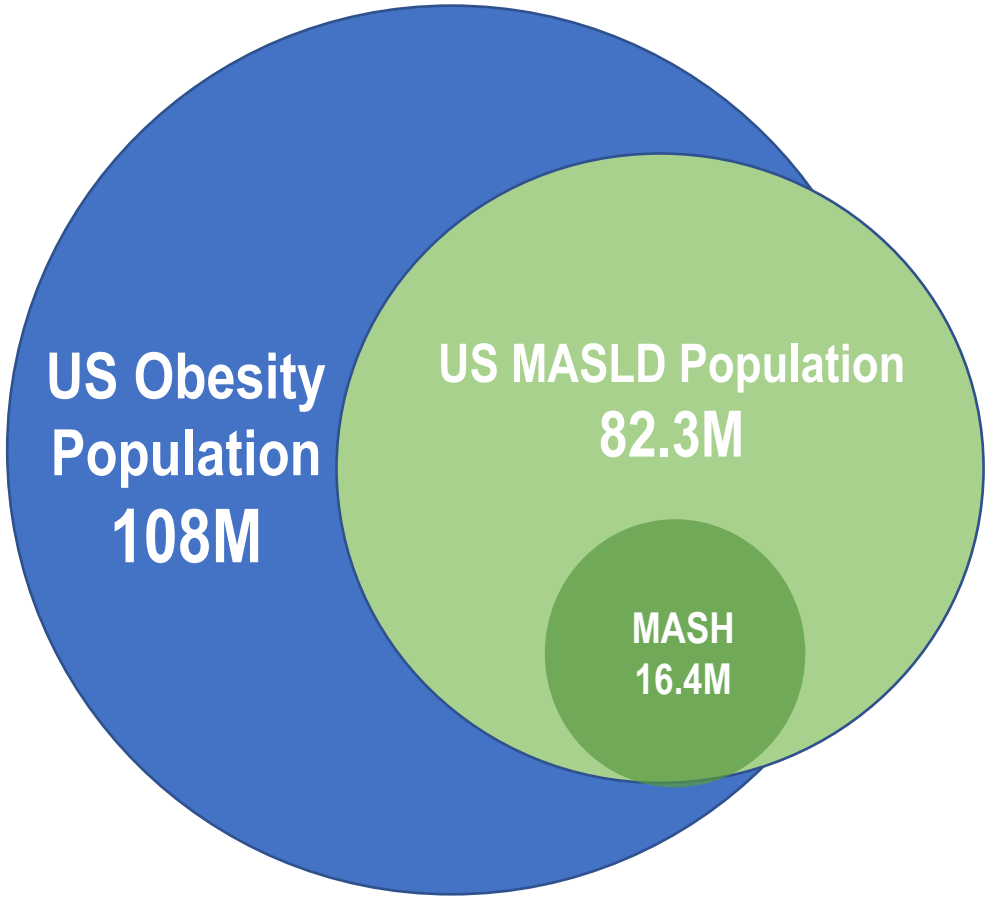
OBESITY AND FATTY LIVER DISEASE

DISEASES WITH UNMET NEED APPROACHING EPIDEMIC PROPORTIONS



The recent successes of semaglutide (Wegovy®) and tirzepatide (Zepbound®) have created optimism for other incretin-based therapies

- GLP-1/GCG dual receptor agonists
- GLP-1/ amylin combination agents
- GLP-1/GIP mAb
- Oral GLP-1 monotherapies

GLP-1: glucagon-like peptide-1
GCG: glucagon
mAB: monoclonal Ab

Hales CM et al. NCHS Data Brief. 2020 Feb;(360):1-8. PMID: 32487284.
Younossi ZM et al all. Gut. 2020 Mar;69(3):564-568.
https://liverfoundation.org/liver-diseases/fatty-liver-disease/nonalcoholic-steatohepatitis-nash/

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OBESITY-RELATED CO-MORBIDITIES ARE THE MOST FREQUENT CAUSE OF DEATH IN PATIENTS WITH MASLD

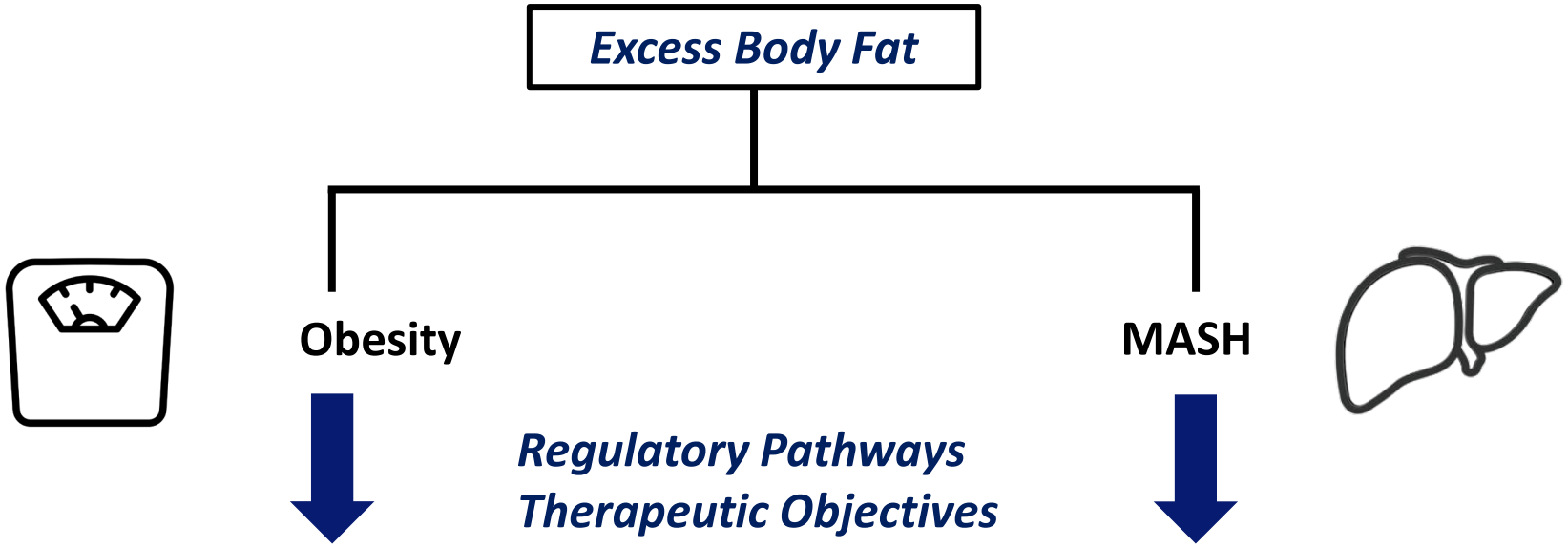
Outcome	n (%)
Death or liver transplantation	193 (100.0)
Cardiovascular disease	74 (38.3)
Non-liver cancer	36 (18.7)
Cirrhosis complications	15 (7.8)
Infections	15 (7.8)
HCC	2 (1.0)
Liver transplantation	1 (0.5)
Other	35 (18.1)
Unknown	15 (7.8)

619 patients with biopsy confirmed MASH

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

OBESITY AND MASH SYNERGIES

DISTINCT REGULATORY PATHWAYS BUT SIMILAR THERAPEUTIC OBJECTIVES



- **Reduce body weight**
- Improve serum lipid profile
- Reduce cardiovascular risk factors

- **Reduce liver fat**
- Reduce liver inflammation
- Reduce body weight

NON-INCRETIN AGENTS FAIL TO ACHIEVE MEANINGFUL WEIGHT LOSS

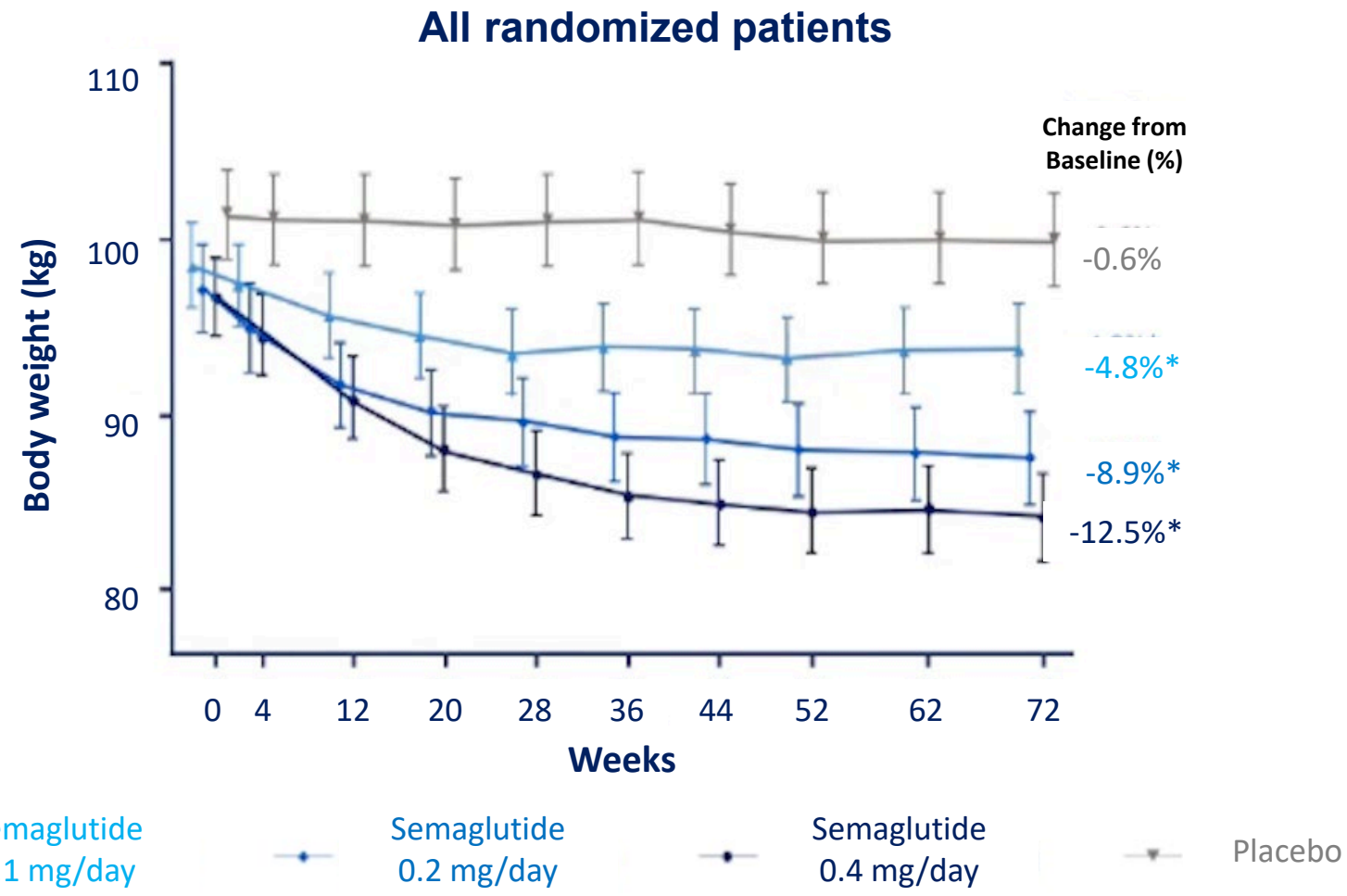
SNAPSHOT OF COMPOUNDS IN ADVANCED MASH DEVELOPMENT

Agent	Mechanism	Change in Body Weight	MASH Resolution	Fibrosis Improvement
Obeticholic acid	FXR agonist	-2%	No	Yes
Resmetirom	THRβ agonist	no change	Yes	Yes
Lanifibranor (1200 mg)	PanPPAR	+3.1%	Yes	Yes
Pegozafermin	FGF21 agonist	-0.6%	Yes	Yes
Efruxifermin (70 mg)	FGF21 agonist	-2.6%	Yes	Yes

Younossi, YM 2019, Lancet 394: 2184-96; Harrison, SA 2019, Lancet 394: 2012-24; Harrison SA 2022 , AASLD, The Liver Meeting 2022; Franque SM, 2021; NEJM 385: 1547-57

SEMAGLUTIDE—WEIGHT LOSS IN PHASE 2 MASH CLINICAL TRIAL

SUBJECTS WITH AND WITHOUT DIABETES



Newsome PN 2020, DOI: 10.1056/NEJMoa2028395

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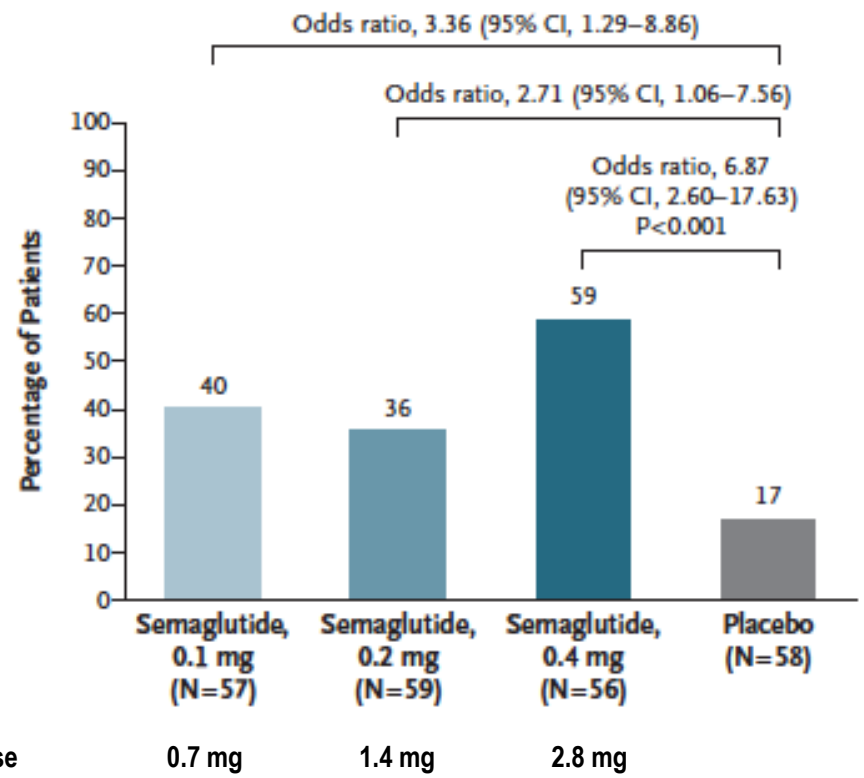
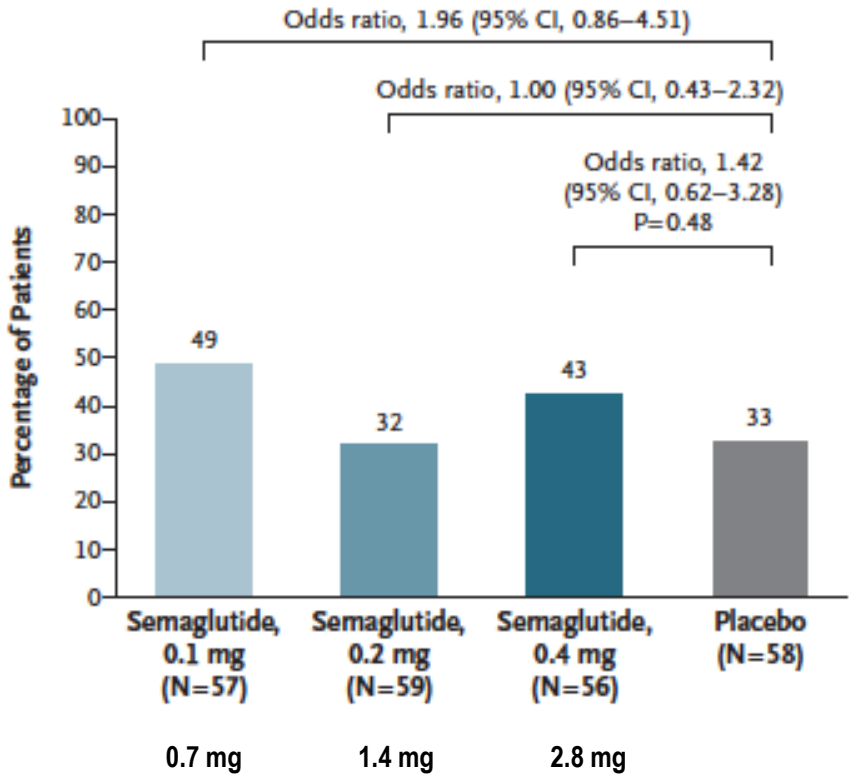
SEMAGLUTIDE—MASH RESOLUTION WITHOUT FIBROSIS IMPROVEMENT

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

MASH Resolution



Fibrosis Improvement



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

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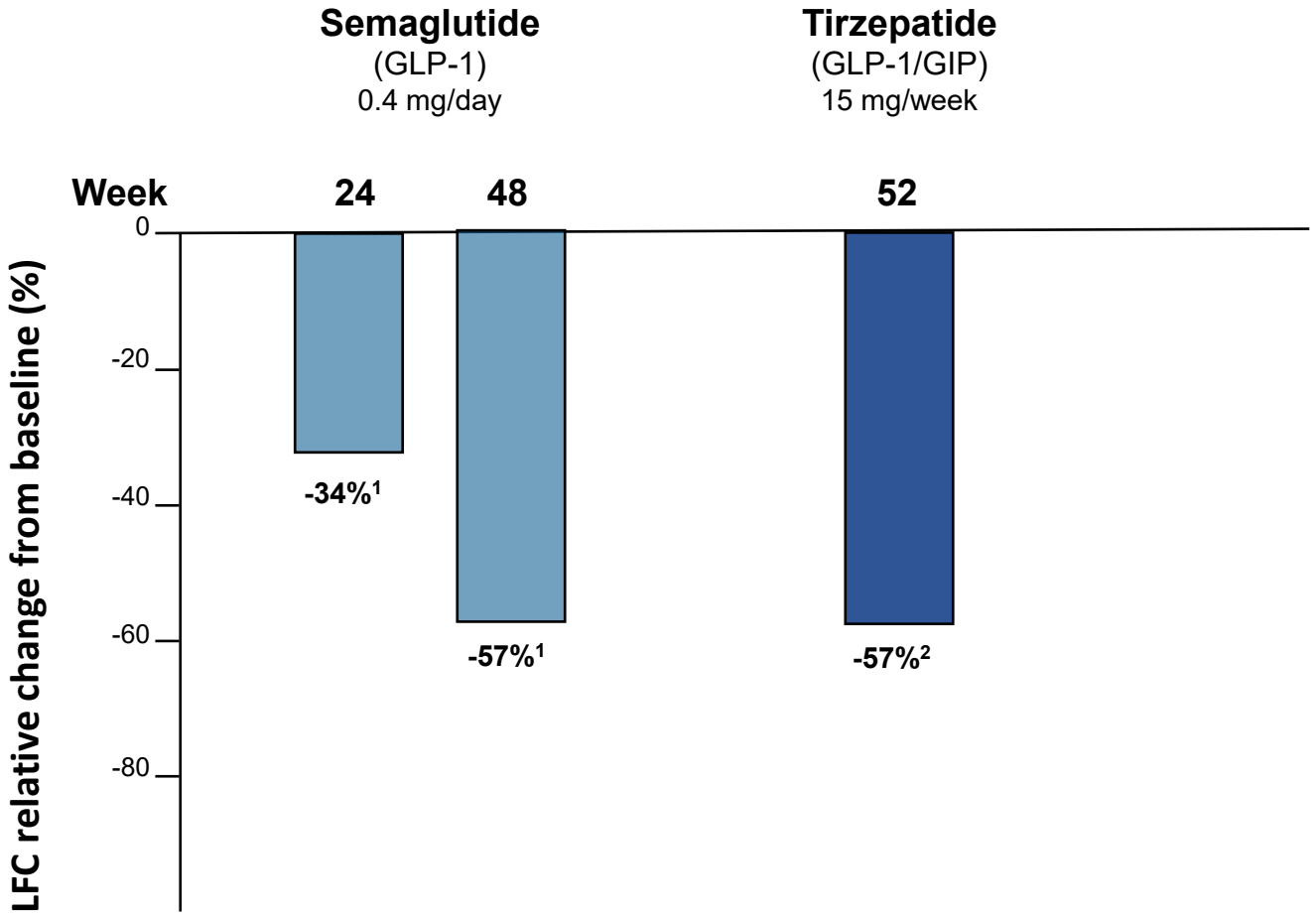
GLP-1 AND GIP AGENTS HAVE ONLY MODEST EFFECTS ON LIVER FAT CONTENT

EFFECTS DRIVEN BY SOLELY BY WEIGHT LOSS DUE TO ABSENCE OF GLP-1 AND GIP RECEPTORS IN LIVER



[1] Flint, Aliment Pharm Ther 2021; [2] Sanyal EASL 2024

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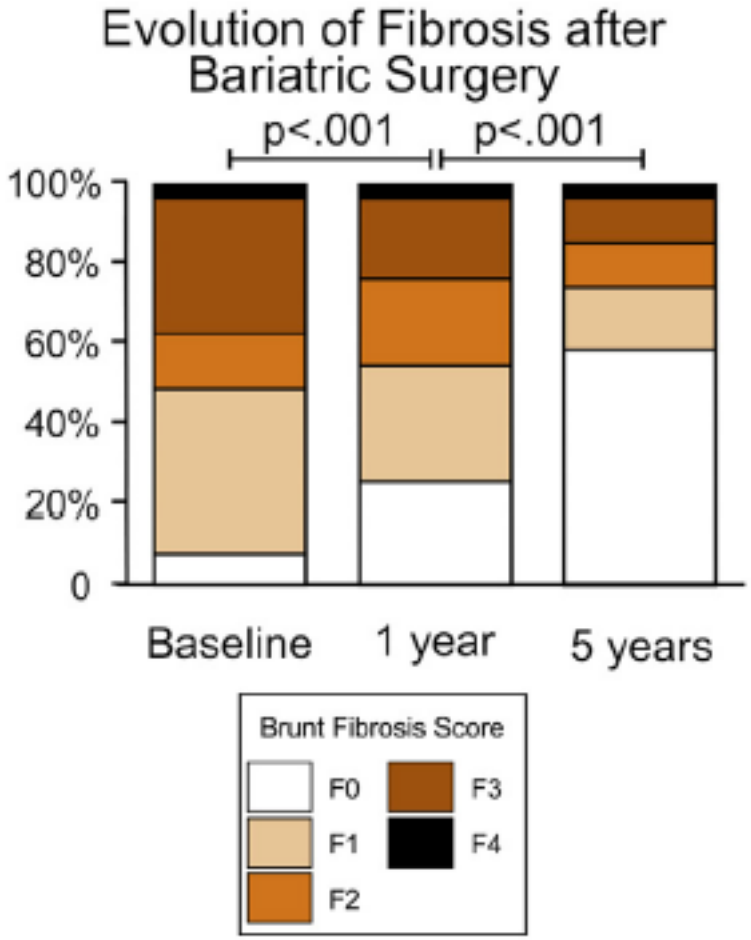
THE IMPACT OF WEIGHT LOSS ON LIVER FIBROSIS MAY BE SLOW

IMPROVEMENT ON FIBROSIS MAY TAKE AS LONG 5 YEARS IN THE ABSENCE OF DIRECT LIVER EFFECTS



Lassailly Gastroenterology 2020

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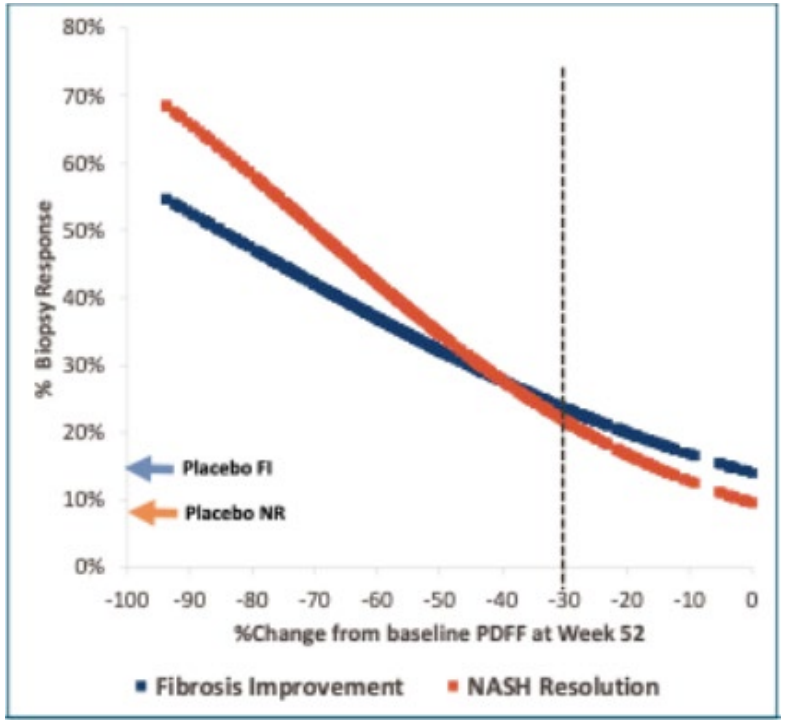
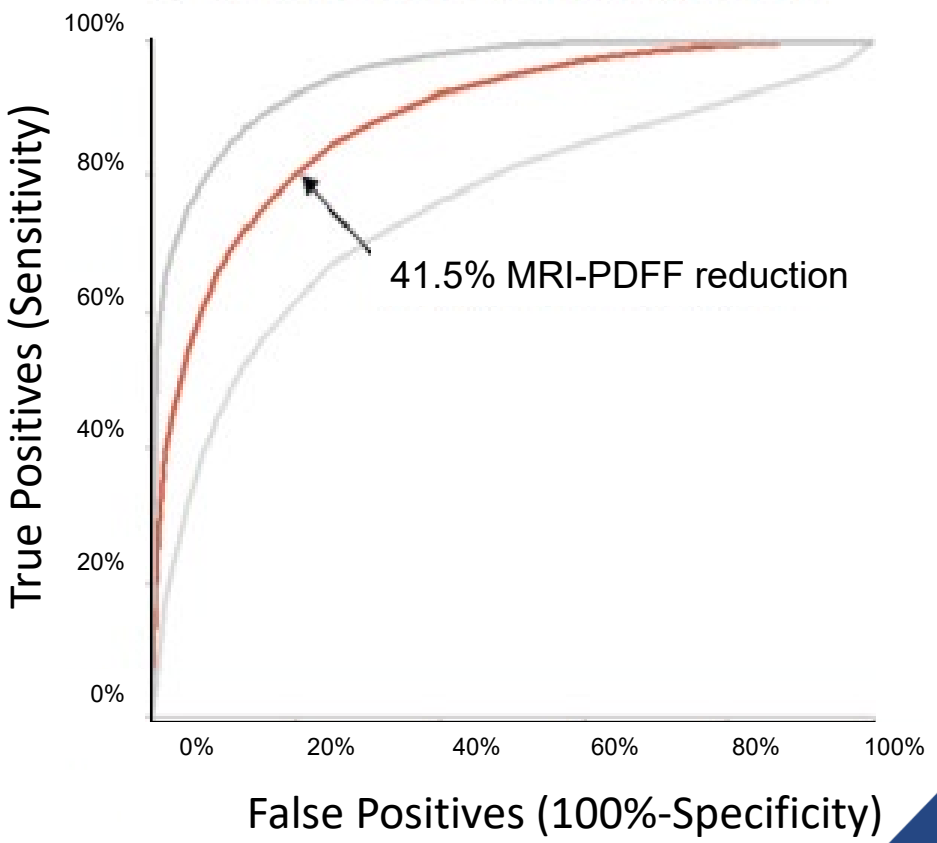
MRI-PDFF REDUCTION STRONGLY PREDICTED OF BIOPSY RESPONSES ON NASH RESOLUTION AND FIBROSIS IMPROVEMENT

Relationship of Δ MRI-PDFF and Biopsy Response



Receiver Operating Curve (ROC)



Noureddin, EASL 2024 and Loomba, EASL 2020

FIBROSIS IMPROVEMENT DRIVEN BY LIVER FAT REDUCTION

Fibrosis Improvement Achieved

Compound	Dose	Mechanism	Liver Fat Reduction	Duration of Treatment	Fibrosis Improvement		
					Treatment	Placebo	Δ
Resmetirom	100 mg QD	THR-β	48%	52 weeks	26%†	14%	12%
Pegozafermin	44 mg Q2W	FGF21	54%	24 weeks	27%†	7%	20%
Tirzepatide	15 mg QW	GLP-1/GIP	57%	52 weeks	51%	30%	21%
Survodutide	6.0 mg QW	GLP-1/GCG	64%	48 weeks [2]	42%	18%	24%
Efruxifermin	50 mg QW	FGF21	64%	24 weeks	41%†	20%	21%
Pemvidutide	1.8 mg QW	GLP-1/GCG	75%	24 weeks	TBD	TBD	TBD

Fibrosis Improvement Not Achieved

Compound	Dose	Mechanism	Liver Fat Reduction	Duration of Treatment	Fibrosis Improvement		
					Treatment	Placebo	Δ
Semaglutide	0.4 mg QD	GLP-1	30-35%[1]	72 weeks	43%	33%	10%

† $p < 0.05$ [1] Estimated at Week 24; [2] ITT analysis

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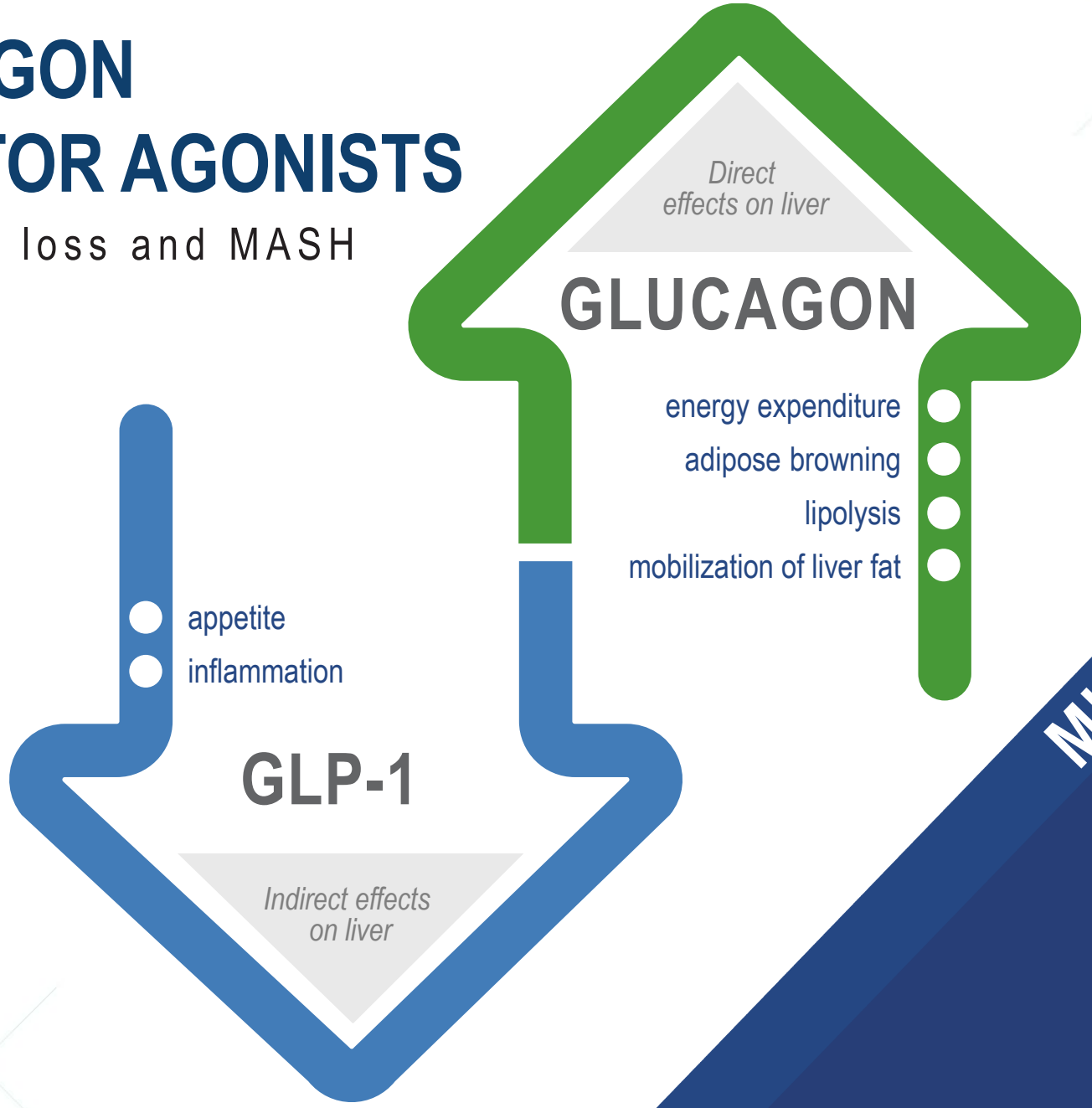
GLP-1/GLUCAGON DUAL RECEPTOR AGONISTS

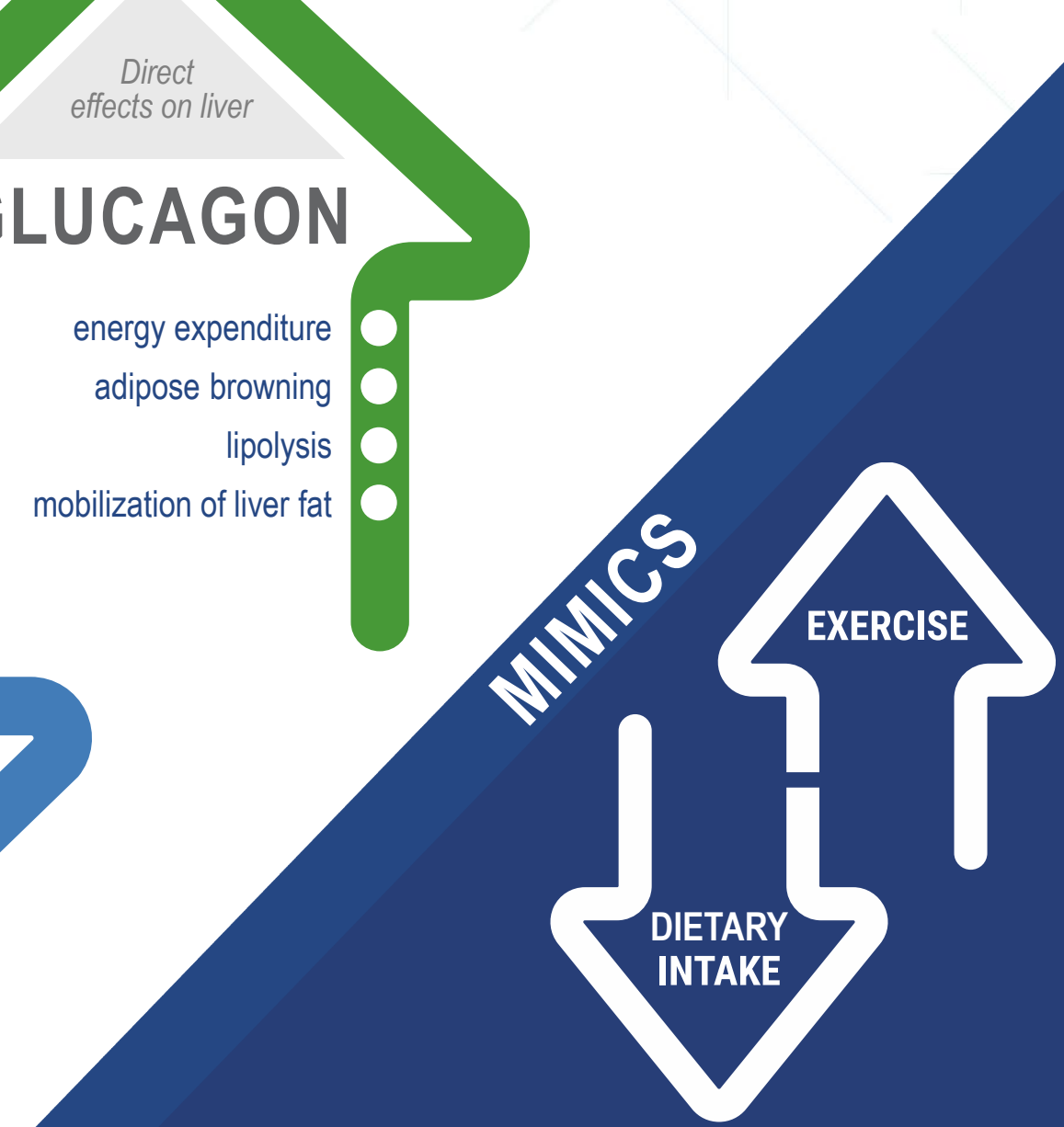
Optimized for weight loss and MASH

Designed for significant reductions in:

BODY WEIGHT

LIVER FAT, INFLAMMATION, & RESULTING FIBROSIS

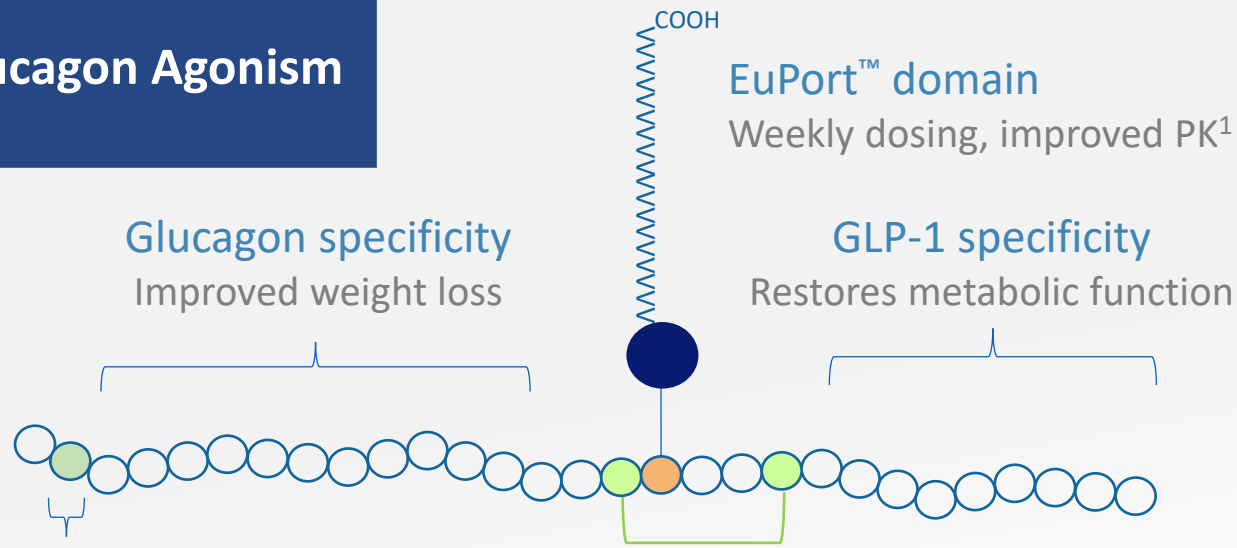




PEMVIDUTIDE

BALANCED AGONIST WITH PROLONGED SERUM HALF-LIFE AND DELAYED TIME TO PEAK CONCENTRATION

Pemvidutide:
Balanced GLP-1: Glucagon Agonism



[1]Nestor JJ et al, Peptide Science. 2021;113:e24221

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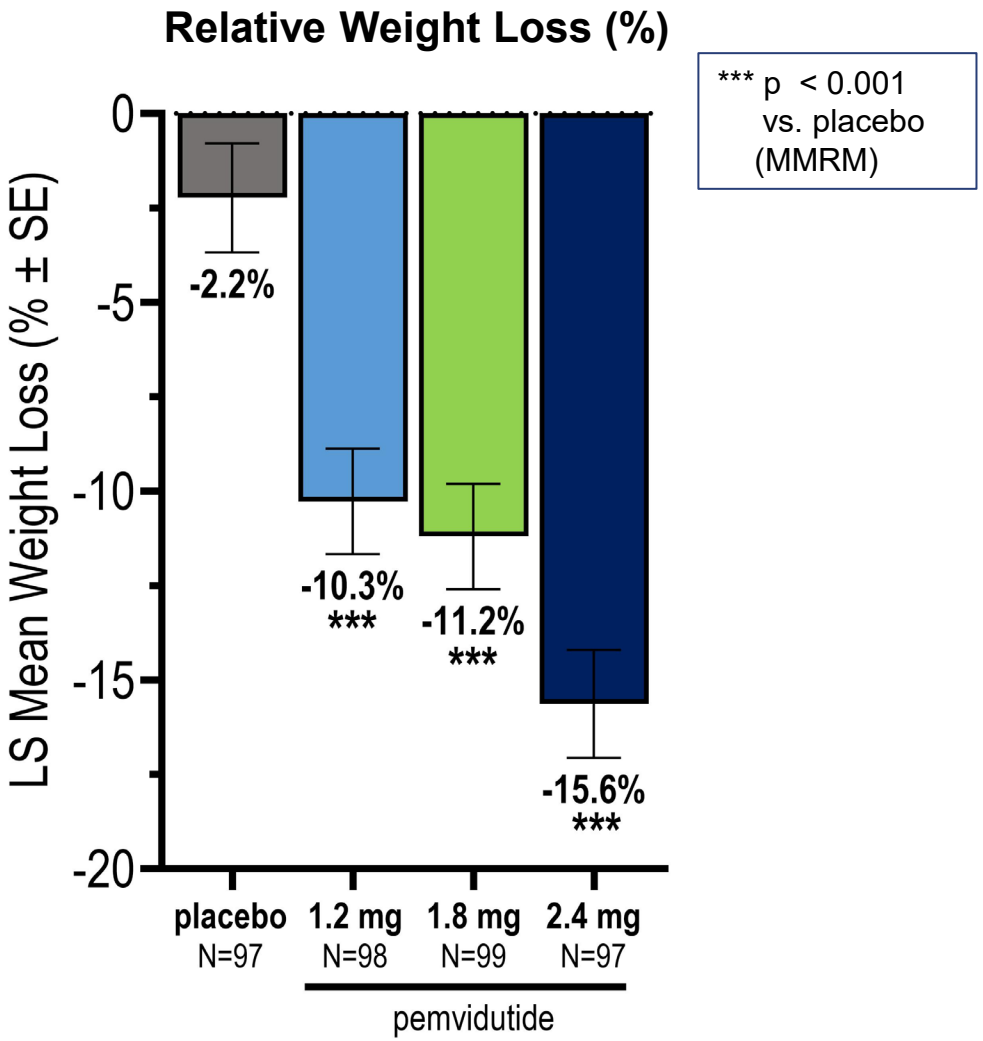
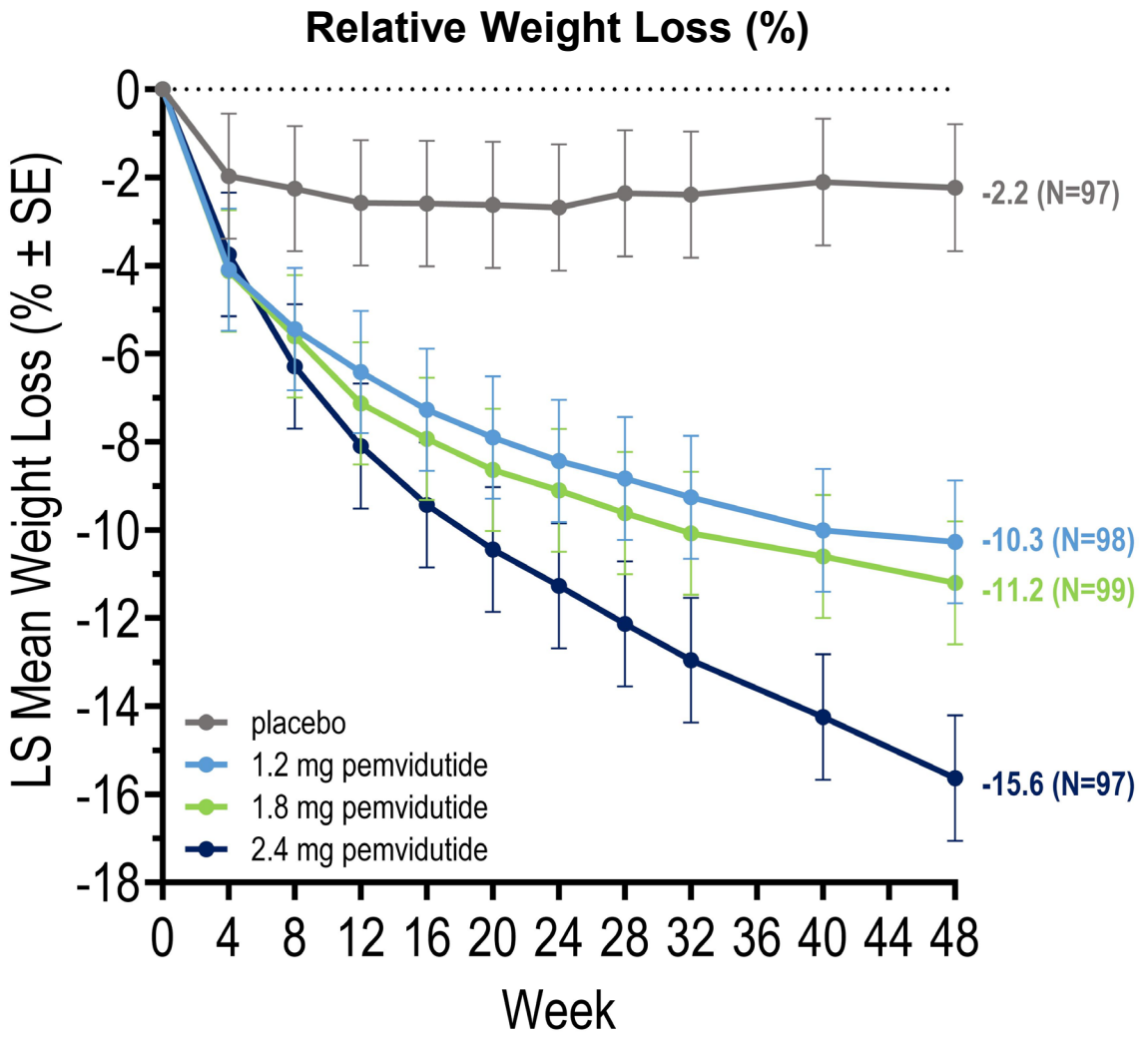
Weight Loss of 15.6% Achieved at Week 48 on 2.4 mg

MEAN WEIGHT LOSS OF 32.2 LBS AND MAXIMAL WEIGHT LOSS OF 87.1 LBS





MMRM, mixed model for repeated measures

PEMVIDUTIDE—CLASS-LEADING EFFECTS ON LEAN MASS PRESERVATION

POTENTIALLY SUPERIOR TO THE 25% LEAN LOSS ASSOCIATED WITH DIET AND EXERCISE[1]

LEAN LOSS INDEX

Drug	Study	Study duration	LBM loss index
Pemvidutide	MOMENTUM Phase 2	48 weeks	21.9%[2]
Tirzepatide	SURMOUNT 1 Phase 3	72 weeks	26.0%[3]
Retatrutide	Phase 2 obesity study	36 weeks	37.7%[4]
Semaglutide	STEP-1 Phase 3	68 weeks	39.9%[5]

Lean loss index = loss of lean mass/total mass loss

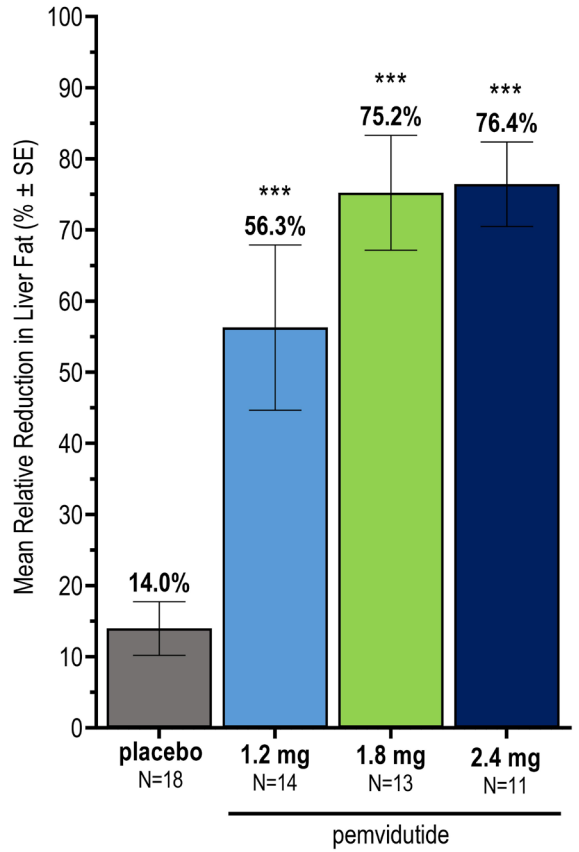
Excessive loss of lean mass has been associated with sarcopenia and bone fractures[5]

1. Heymsfield Obes Rev. 2014 April; 15(4): 310–321; 2. Aronne LA, 84th ADA Meeting, June 2024; 3. Kushner RF, Obesity Week 2022; 4. Harris C, Obesity Week 2023; 5. Wilding JPH, et al. N Engl J Med. 2021 Mar 18;384(11):989-1002.

PEMVIDUTIDE— ROBUST REDUCTIONS IN LIVER FAT CONTENT AT 24 WEEKS

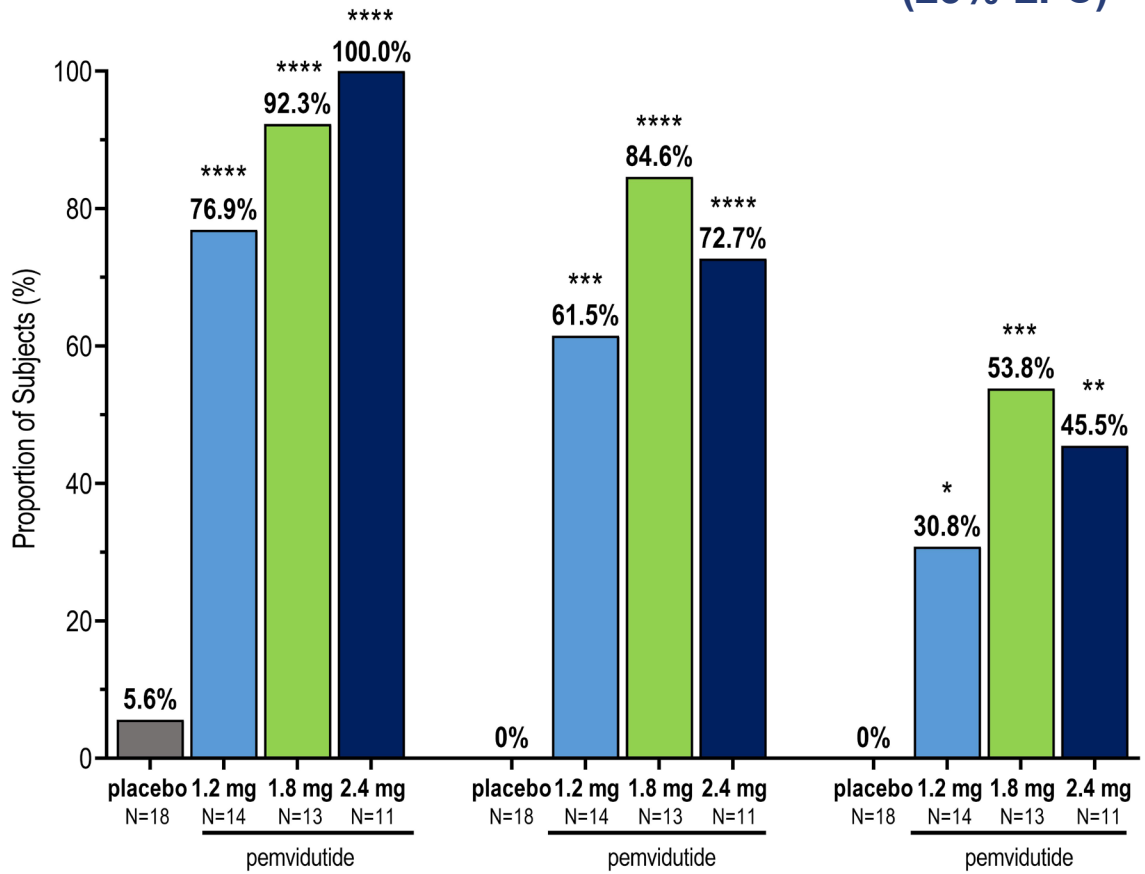
CORRELATES WITH MASH RESOLUTION AND FIBROSIS IMPROVEMENT

Relative Reduction



*** p < 0.001 vs placebo ANCOVA, LS mean ± SE

30% Reduction 50% Reduction Normalization (≤5% LFC)



* p < 0.05, *** p < 0.001, ****, p < 0.0001 vs placebo, Cochran-Mantel-Haenszel

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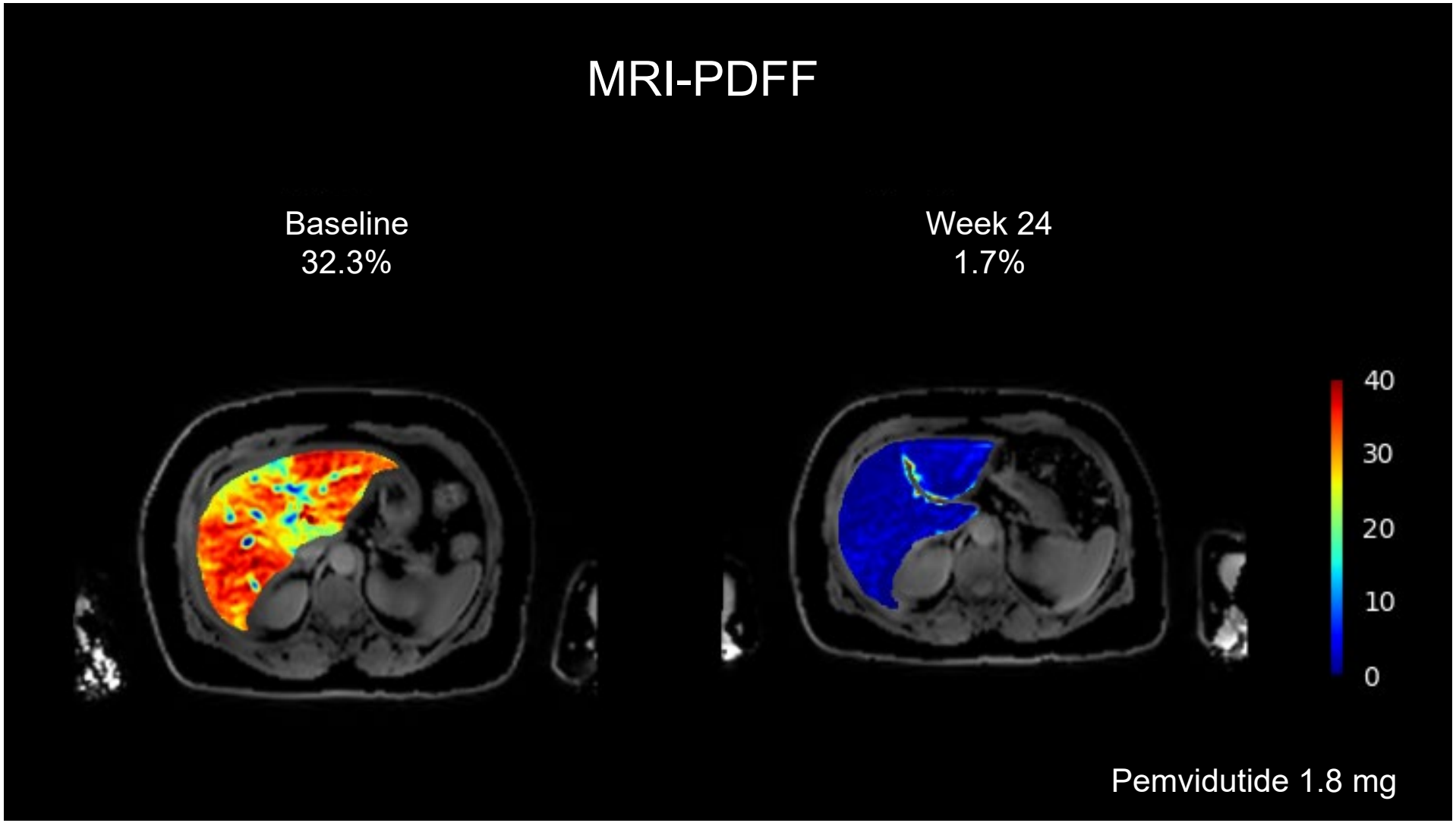
PEMVIDUTIDE— MARKED REDUCTION OF LIVER FAT CONTENT BY MRI-PDFF AT WEEK 24



This reduction was accompanied by a 38.1% decrease in liver volume

Study ALT-801-106 MASLD Trial

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GLP-1 BASED AGENTS IN DEVELOPMENT[1] FOR MASH AND OBESITY

HIGH GLUCAGON CONTENT DRIVES POTENT EFFECTS ON LIVER FAT AND BODY WEIGHT

Agent	Class	Agonist Ratios[2]	Dose Titration	LFC Reduction	Weight Reduction
Semaglutide	GLP-1	—	yes	+	++++
Tirzepatide	GLP-1/GIP	1:15	yes	+	++++
Cotadutide	GLP-1/GCG	5:1	yes	++	+
Retatrutide	GLP-1/GIP/GCG	1:6:0.1	yes	++++	++++
Survodutide	GLP-1/GCG	8:1	yes	+++	+++
Efinopegdutide	GLP-1/GCG	2:1	yes	++++	++++
Pemvidutide	GLP-1/GCG	1:1	no	++++	++++

[1] Phase 2 and later; [2] based on cell-based potency assays
GLP-1, glucagon-like peptide-1; GIP, gastric inhibitory polypeptide; GCG, glucagon

PEMVIDUTIDE— DIRECT ANTI-FIBROTIC EFFECTS IN PRECLINICAL MODEL OF HEPATIC FIBROSIS

- Significant improvement in a model of chemically-induced hepatic fibrosis after 14 days of treatment with pemvidutide
- The model excluded the effects of liver fat reduction, providing evidence for a direct effect of pemvidutide in reducing liver fibrosis

THANK YOU